BIOASSEMBLER

Integrating bio-inspired assembly into semiconductor manufacturing technology for biosensors

Assessment of the Photolithographic Synthetic Chemistry Market

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Summary

This document provides an overview of the biosensors market based on existing literature, infographics and patent information. It highlights the structures and dynamics of the biosensors and photolithography market worldwide, with an emphasis on the state of the art in the European Union and the differences between the macro-regions of the global market.

The literature review and biosensors market chapters trace past developments in the field and examine the evolution of biosensors in four different parameters: the type of technology, the type of product, the industry applications and the region of manufacturers.

Forecasting the potential of biosensors provides a framework for future technologies, applications and production methods in the field. The proliferation of clean room facilities and the diversification of applications have contributed to the steady growth of biosensor supply, resulting in lower demand-side costs and innovation in the development of the photolithography market.

The possible outcomes and recommendations section provides conclusions based on the overview analysis of the biosensors field. It also provides an insight into the most relevant projects in the biosensors market, whilst reflecting on the challenges and bottlenecks to implementing this technology.

The future of biosensors has great potential. Sustainability and convenience are two of the main priorities manufacturers define to increase the market value of microelectromechanical sensors; therefore, the BioAssembler multiplex model can accelerate this innovation process.

Keywords

Biosensors; Photolithography; Market Analysis; Sustainable Innovation; Technology Production

1. Introduction

Biosensor technology has massively expanded in recent decades (Ramirez et al., 2022). From smartphones to PCR tests, biosensors are crucial for collecting data that can help societies evolve through a digital transition, where it will be easier and more cost-effective to track health conditions or monitor food quality. The production of biosensors is a delicate process that needs to be optimised to achieve a stable and reliable massification of the technology (Guo et al., 2022), which considers sustainable development goals as one of its fundamental features. Therefore, the BioAssembler project is working on a bio-inspired assembly technology for scalable manufacturing of silicon-based label-free multiplexed biosensors, using photolithography as the main manufacturing component.

The photolithography method is widely used in the semiconductor industry (Karunakaran et al., 2015). However, the BioAssembler project is taking an innovative approach to the industrial production of these biosensors. The BioAssembler consortium supports the possibility of rapid and massively parallel integration of biomolecules on silicon wafers, which can revolutionise the production of biosensors in Europe. The fabrication of microelectromechanical sensors (MEMS), mass resonator wafers, DNA synthesis on the sensor surface, the production of DNA-labelled antibodies and the evaluation of biosensor chips in multiplexed bioassays are all features of the production process that BioAssembler aims to implement. These parts of the process are not independent of the industrial and environmental risks associated with introducing technological innovation into the chemical market. To address these issues, the BioAssembler project has a transversal concern to assess the financial, environmental and ethical requirements that may arise from this new model of biosensor production.

This report is one of the tasks related to Work Package 4 of the project and aims at understanding the market trends in the field of photolithography and biosensors, which will be complemented by the socioeconomic analysis of the technology to be developed by Work Package 5 and 6. This analysis will be carried out through the available data on the biosensors market, the European Patent Office (EPO) database and the academic dynamics generated between competences, researchers and institutions/countries (through the data available in the Web of Science platform) that gravitate around these industries. The aim of this report fits into the general framework of Work Package 4 to bring a social sciences and humanities approach

(Sørensen, 2009) to the study of zipcode sequence design for photolithography-based manufacturing.

The BioAssembler Work Package 4, coordinated by Prof. Mark Somoza from the University of Vienna, focuses on the DNA zipcode process. The work package is divided into the various laboratory steps that contribute to photolithographic DNA synthesis, including testing on the glass substrate and the optical system at the wafer level. This scientific effort of the consortium to work on the DNA synthesis market, which is the premise of Work Package 4, will be additionally complemented by the CES team through a socioeconomic analysis. The inclusion of CES in this Work Package allows the analysis of a social science theoretical background related to the technological and innovation processes behind biosensor production.

The structure of this report starts with a brief overview of biosensors, including an introduction to the technology, followed by a historical context highlighting the most influential actors and processes that led to the introduction of photolithography in the semiconductor industry.

The literature review will shed light on the latest advances in the academic bibliography related to biosensors, with a section specifically dedicated to analysing the theoretical framework that examines the partnerships between industry and academia in the innovation sector. The next section is an introduction to the biosensors market, organised by possible application areas, considering the latest trends in the literature. This is followed by a methodological section explaining the methods used. Then the networks of competences, authors and organisations/countries are drawn. The discussion section is based on a forecasting exercise based on trends in the biosensors production market. Finally, the conclusion draws recommendations based on the current state of the market and highlights the importance of gathering different theoretical backgrounds in producing scientific and technological results.

2. A Brief Overview on Biosensors

2.1 The potential of label-free multiplex biosensors

The potential to introduce a bio-inspired assembly technology in the European Union market for scaling-up production of label-free multiplex silicon-based biosensors, as proposed by the BioAssembler research project, contributes to the evolution of different industries. Expanding the biosensors market will affect other activities implementing biosensors as monitoring methods in the respective fields.

The diagnosis services previously provided only in hospitals and health facilities penetrated the domestic domain with an associated massification of these biosensing devices. For example, in the USA the biosensors market grew over 200% during the pandemic years; there is an estimated compound annual growth rate of 7.5 for the following years until a total of 3.2 billion dollars by the end of 2026 (MarketsandMarkets, 2021).

This massification resulted in similar advances in the literature in the field. New research paths have been developing bibliometric analysis on state-of-the-art related to biosensing devices usage and the number of patents in the last decades (Gonçalves et al., 2019; Sales et al., 2023; Yunus et al., 2023). This report draws on this bibliometric and patents analysis model to illustrate the evolution of the biosensors market in four different components: 1) the type of technology, 2) the type of product, 3) the industry applications and 4) the production region. These components are frequently discussed in biosensor literature and industrial reports; thus, it is an appropriate tool for structuring the market dynamics assessment.

The planetary dimension that issues such as environmental sustainability and quality of life have obtained during the last decades in civil society is mirrored in the evolution of the biosensing field. Furthermore, this explains why there has been an active concern about creating new environmentally friendly devices. The Green chemistry approach addresses these challenges by developing new synthetic schemes and apparatuses that simplify chemical production processes, as well as exploring eco-friendly greener solvents that maximise desired products and minimise by-products (Li & Trost, 2008).

Simultaneously, there is a need to rehabilitate nanotechnology with quicker and more accurate results, using devices that enable data collection with minimal intrusion. Wearable devices have gained influence in the biosensors market and literature, as they are the most recent example of non-invasive progress in monitoring technologies (Sempionatto et al., 2019). The multiplex electrochemical sensors, such as the ones the BioAssembler envisions creating, are optimally designed to promote a more sustainable and efficient market.

Furthermore, the project seeks to develop innovative strategies to establish a science-society linkage involving multiple social actors, such as environmentalists, farmers, students, and policymakers, and contribute to advancing science policies. This market analysis is fundamental to understanding the financial feasibility of such innovation and the receptiveness of such technology by the general population. This includes tracking similar devices that may have been released recently, potentially complicating the market introduction of the BioAssembler product.

The field's expansion leads to new challenges posed by biosensors' considerable popularity in recent years. The growing demand for home-based healthcare, the adaptation to new competencies and application areas, and the legislative effort to frame the domains of biosensing implementation are external factors that must be weighed when delving into the market complexity of such nanotechnology and will be addressed as recommendations by the end of this report.

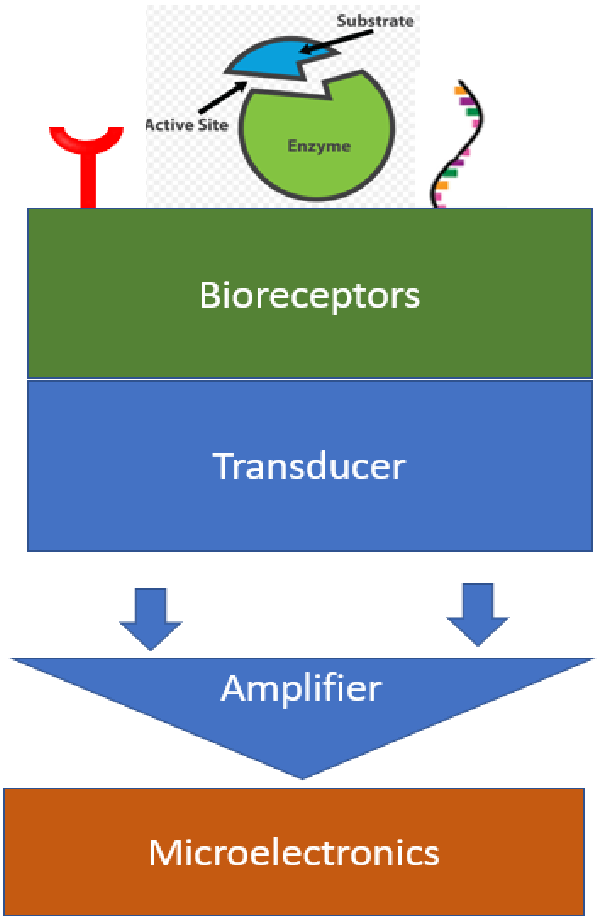
This deliverable comprises two initial sections introducing the biosensor technology and the production process through photolithography. A second part of the report is devoted to comprehending the state-of-the-art, which includes a brief understanding of the most recent research on biosensors, focusing on the innovation partnerships between industries and universities to develop nanotechnology.

The following section discusses the various markets biosensors have reached in the last decades, ranging from the chemical industry to forensics and security. This bridges the contextual matter about the technology and the methodology chapter, where the framework of the bibliometric analysis is explained, and the networks' maps are displayed. After determining the most critical competencies, geographical markets and organizations for the biosensor's realm, there is an effort to draw recommendations and forecast the future of the technology based on the current state-of-the-art. The deliverable ends with a conclusion section with a positive tone based on the literature and recent trends about the prospective uses of biosensors and how collaboration between Exact Sciences, Natural Sciences and Social Sciences and Humanities can help reach the proposed goals in innovation-related projects.

2.2 The Technology

A biosensor (Figure 1) is a sensor where a bioreceptor is connected to a transducer, a device that can convert the bioreceptor response into a measurable signal, most commonly an electrical signal. An enzyme or a binder, such as single-stranded DNA probes, an antibody, aptamers, or molecularly imprinted polymers (MIP), can work as a bioreceptor (Majdinasab et al., 2021). DNA and antibodies are naturally both occurring binders found in living organisms. DNA strand selectively binds to a complementary DNA strand to form a duplex (Bhingardeve et al., 2020). Antibodies are natural defence responses produced by an organism against intruders. They bind the intruder selectively, for example, proteins on the virus surface or a toxic substance such as cocaine or pesticide. Aptamers and Membrane Proteins are artificially produced alternatives to antibodies (Mahmud et al., 2023).

Figure 1. Biosensor Components



Source: Biomensio Ltd.

2.3 Typologies of biosensors

DNA sensors

DNA is made of two complementary strands that are connected via hydrogen bonds. Thymine permanently binds to adenine and guanine to cytosine. When one DNA strand (a probe) is immobilised on the transducer surface, it is very selective towards its complementary strand (Pividori et al., 2020). DNA occurs naturally in very low amounts, which is insufficient for most detection methods. However, DNA can be amplified by polymerase chain reaction (PCR). PCR runs in cycles, each cycle doubling the amount of DNA present.

Immunosensors

Immunosensors use antibodies as binders to capture molecules at the sensor surface. They are the most common type of rapid screening tests on the market due to the simplicity of their use (Mollarasouli et al., 2019). Usually, they require only simple instrumentation and produce visually readable results; only a small sample is needed, and the test is fast. The disadvantages of immunosensors are the low level of multiplexing, i.e., the capacity to detect multiple analytes from the same sample, and their low sensitivity and selectivity. The most common type of rapid test on the market is based on lateral flow assay. They comprise nitrocellulose paper, which moves the sample towards the detection lines. On the way, the sample reacts with gold-labelled detection antibodies, which move to the detection area.

Immunoassays, in which antibodies are immobilised on the sensor surfaces, are the most common type of immunosensors in clinical applications and are used to detect the most common analytes. The main exception is small analytes, such as antibiotics, toxins, pesticides and drugs. Due to their small size, they cannot effectively bind to antibodies and must be detected by competitive assay instead. In a competitive assay, the analyte molecules are immobilised on the surface via suitable chemistry (Gosling, 1990). The antibodies are then mixed with the sample that may or may not contain the analyte. Antibodies in the sample bind to the analytes and cannot bind to the surface, whereas in the absence of analytes, all antibodies will bind to the sensor's surface, resulting in a high signal.

Acoustic wave-type sensors

Acoustic wave sensors utilise piezoelectric properties of materials for mass sensing, a phenomenon first described by Jacques and Pierre Curie, who observed that application of a voltage across a crystal causes a corresponding mechanical strain. The strain induces oscillatory motion in the crystal that causes the generation of an acoustic wave at the characteristic resonant frequency. The wave propagates through the crystal in bulk acoustic wave (BAW) devices, whereas it is confined to the crystal surface in surface acoustic wave (SAW) devices. Surface acoustic wave (SAW) sensors typically operate at frequencies between 50 MHz and a few GHz and are used for measuring temperature, pressure, acceleration, concentration, and chemical/biological binding. SAW devices can use quartz, GaAs or LiNbO3 as the piezoelectrical material and interdigitated electrodes for exciting and measuring surface-confined waves. Analyte sizes range from individual, small molecules to large bacteria or even cells (Länge et al., 2008).

In BioAssembler, an efficient method for wafer-level biofunctionalisation is being developed for transducer production. As the model analytes, inflammatory biomarkers in plasma have been selected for the proof of concept. However, once the process is optimised, it can be adapted for the immobilisation of antibodies and thus applicable to any biosensing application utilising immunoassay detection.

Photolithography

Photolithography is a viable method of fabricating microstructures (Ishihara & Luo, 2006) and is commonly employed in the semiconductor industry and mass production of Si-based devices down to several tens of nanometers (Hubenthal, 2011; Tanaka, 2015). Photolithography, also called lithography and microlithography, is an image formation and transfer process which evolved from that used in the printing industry about 200 years ago (Vladimirsky, 1999). Therefore, photolithography is the standard method for fabricating printed circuit boards (PCBs), and microprocessors use light to make conductive paths and electronic components (TechTarget Contributor, 2013).

Photolithography involves using a photomask with a defined shape and size on the substrate to expose selected substrate regions to UV light, thereby removing photolabile groups on the surface. For DNA/RNA microarrays, a designated nucleotide is immobilised, followed by the addition of a blocking agent. This cycle of masking, UV exposure, nucleotide immobilisation, and the addition of a blocking agent is repeated until a desired length of 20–25 nucleotides is achieved. This approach is also known as the *in situ* synthesis method.

2.4 A historical context of the photolithography developers in the production of biosensors

Photolithography has been a widely used production method in biosensor manufacturing due to its versatility and wide-ranging functions. This section delves into the historical context of photolithography, tracing its emergence in North American industries and its subsequent massification and automation.

The origins of photolithography can be traced back to its usage for printed circuits in 1955 (Mirvakili et al., 2019). The technique was also used for silicon wafer processing, initially envisioned by Jules Andrews and Walter Bond and later funded by Bell Labs, the first company dedicated to semiconductors and lithography. The USA Department of Defense took that technology and developed it further, giving it the official name of 'photolithography' (Department of the Air Force, 1986). In the 1960s, the photolithography machine revolutionised chip manufacturing companies, leading to significant advancements in companies such as Texas Instruments, IBM, Motorola and Sony (Hutcheson, 2000).

By 1978, after almost two decades of machine learning and development, GCA Medical Technology Inc. introduced the first automated stepper lithography machine that monopolised the lithography machines' market in the following years until Nikon's first commercialisation of steppers (Fay, 2002). This moment highlighted the definitive entrance of the Asian market into photolithography, reaching the same level as GCA Medical Technology Inc. in 1984. Throughout the years, the application of photolithography expanded from the chip business to the development of the biosensors field.

The history of using photolithography for biosensing applications originates with Affymax, later called Affymetrix (Callinan & Feinberg, 2006). They adapted 1980s microchip technology to make peptide arrays using amino acids with photolabile protecting groups. Peptide synthesis is difficult, so they eventually decided to concentrate on making DNA arrays for genomics applications. The emergence of the GeneChip array structurally changed the study of modern biology. Their DNA arrays were the first instance of a high throughput approach in genomics research (Reuter et al., 2015). Affymetrix chips are available through ThermoFisher, which bought Affymetrix in 2016. Affymetrix started around 1992 and commercialised the concept of the GeneChip array, which made DNA zip coding accessible to universities, pharmaceutical companies, and public-private health organisations.

In 1991, Dr Stephen Fodor, one of Affymetrix's co-founders, and some of his colleagues published a new scope of findings in *Science*, initiating the microarray industry (Fodor et al., 1991). Shortly after, in 1994, the first DNA microarray prototype was commercialised, which led to the production of the GeneChip Scanner, based on Affymetrix's knowledge, a user-friendly desktop platform for microarray production (Yoshioka et al., 2000).

A few years later, some researchers at the University of Wisconsin realised they could improve DNA microarray. They took advantage of a recent Texas Instruments (TI) invention, the Digital Micromirror Device (DMD). TI developed the DMD (often now called DLP - Digital light processor) for displaying video, and most cinemas now project with DMD technology. The advantage of using the DMD in DNA microarray synthesis is that the micromirrors can replace chrome masks to direct the light necessary for microarray synthesis, simplifying the process significantly (Agbavwe, 2011).

During the same period, a better photolabile group developed at the University of Konstanz could be employed to improve the synthesis chemistry and make it much more efficient. The synthesis of DNA microarrays using DMD-based technology was developed commercially by a start-up called NimbleGen in 1999 (McCormick & Nuwaysir, 2005). NimbleGen was bought by Roche in 2007, becoming Roche-NimbleGen, and started to produce multicolour hybridisations. Around the same time, a German company called Febit developed similar technology but faced competitiveness challenges and ended up closing in 2004 (Sussman, 2003).

The advent of next-generation sequencing put much pressure on manufacturers of DNA microarrays impacting their market share. As a result, Roche closed NimbleGen in 2012, redirecting their investments towards developing sequencing technology. The technology was transferred to a new Roche spinoff called Nimble Therapeutics, which uses the same basic technology but applies it to synthesising peptide arrays, just like Affymetrix's earlier attempts (Mishra et al., 2021). The central Universities involved in this advancement were the University of Wisconsin-Madison and the University of Konstanz in the Western world, which have competed for the largest share of the market with Chinese universities.

2.5 The State-of-the-Art and the technical evolution of microelectromechanical biosensors

The growth of photolithography and the advancements in biosensor production methods have driven the evolution of the Microelectromechanical sensors (MEMS) industry. The literature has also followed the developments from the three generations of biosensors already in the market and scrutinised the infinite possibilities of biosensors' application to diverse tasks.

The first generation of biosensors, the bioreceptor, is physically enclosed behind a dialysis membrane near the base sensor. As generations progress, a covalent bond is used to immobilise a transducer interface or incorporate a polymer matrix at the transduction surface. When the second generation of components remains independent (control electronics—electrode—biomolecule), the third generation significantly advances as it adds a bioreceptor molecule to the base sensing element (Lee & Mutharasan, 2005). Initially designed for enzyme electrode systems, these definitions may apply to biosensors. Most development effort goes into the second and third generations (Hamzah & Nadzirah, 2022). Entities that contribute to the progress of knowledge and production processes in the biosensors field can be divided into three main groups: 1) the specialised manufacturers, 2) start-ups and small manufacturers and 3) large national and multinational companies (Robinson et al., 2013). Moreover, the frequent presence of universities and think tanks in the teams dedicated to developing biosensors built an interdisciplinarity scientific spirit around this field of innovation (ibid.).

The avenues identified in the literature for biosensor innovation are based on two primary principles. Firstly, the exploitation of biorecognition potential using nanostructured materials will require a change in the composition of the biosensors, with particular emphasis on surface redimension. The other possible path forecasted for biosensor innovation involves an active role of the producers in the field in finding new transducer possibilities with new materials. Some examples in the literature include the quantum effects and the piezoelectric effect. A new research path that has gained traction is using synthetic materials in the biosensor's composition. Using synthetic enzyme biosensors has become lead progress and provides a sustainable option to the natural enzymes extracted by animal samples. These advances, complemented by establishing cell-free synthetic biology for sensing devices (Karig, 2017), constitute a sophisticated method to obtain quicker and environmentally friendly diagnosis.

The production process through synthetic photolithography has been getting more room in the MEMS market lately. The possibility of reinforcing the sustainability of the semiconductors market by applying synthetic photolithography explains the growth of this production method. Moreover, the higher demand for electronic devices and the massification of internet usage in all formats require an increase in the market share of photolithography equipment (Straits Research, 2021). Wearable devices, virtual reality, smart homes, Artificial intelligence and 4k technology demand more production from the most prolific manufacturers in the field. Therefore, the market share of companies such as ASML Holding, Canon, Nikon Corporation or SÜSS Microtec SE, after experiencing a backlash during Covid-19, is now growing at a steady pace with a photolithography equipment market expected to achieve a constant annual growth rate of 5,1% during the 2020-2030 period (Straits Research, 2021).

2.6 Innovation and university-industry partnerships

There is a growing literature on the innovation processes established between universities and industries (Cai, 2022) that Horizon Europe programmes have incentivised as a response to the most recent global challenges, such as Covid-19. The results are significant in explaining the university-industry collaboration as one of the driving forces of a country's ability to develop programmes of R&D (Usman, 2017). The positive impact of these partnerships is more notorious in developed countries (Usman, 2017; Tseng et al., 2020), raising concerns regarding the technology development gap' widening between countries (Usman, 2017). The literature about collaboration between industry and academia emphasises the university as one of the most significant actors in the knowledge exchange networks (Zukauskaite, 2012).

Building innovative technologies in the university environment is motivated by curricular valorisation, commercialisation potential and university incentives (Daniel & Alves, 2020). Nonetheless, some bottlenecks prevent this collaboration and the production of new technologies in an academic environment - the lack of flexibility in university procedures and the negotiation process with industries, the obstacles to R&D investment and the marketing associated with it, and low market potential for the patents built in universities by lack of financial or intellectual capacity of the enterprises (ibid.).

Developing industrial and commercial markets based on a dynamic of sharing innovative and technological products, produced mainly inside R&D environments in public and private research centres and enterprises (Snir, 2014), makes the quantitative bibliometric analysis of this report fundamental to detect the most highlighted skills in the field. The technology linkage model investigates the science and technology collaborations and innovation transfer (Yang et al., 2021) and has allowed scholars to map the evolution of the nanotechnology field with a focus on the role of governments, enterprises and universities (Porter & Cunningham, 2004). It also permits the assessment of the gaps in the global nanotechnology market that the countries' national authorities can tackle by investing in improving the most valuable competencies.

From the knowledge acquired by past research on the biosensors topic, there is exponential growth in the Asian market production; nonetheless, the BRICS (Brazil, Russia, India, China and South Africa) (Fogel & Limson, 2016) have overthrown the strong position of Japan in the last century through new Science, Technology, Engineering and Mathematics (STEM) networking mechanisms based on the absorption of research know-how in regional clusters (Fukugawa, 2016). The partnerships established by Chinese companies considered latecomer firms with research centres in developed countries such as Germany (Liefner et al., 2019) or the solid investment of the Chinese government in the patent production of nanotechnology in public universities contributed to the growth of China in the last two decades (Huang & Wu, 2011).

The USA and the European Union remained the field's second and third most prolific markets since the 90s. However, the gap to the Asian market has widened in the evolution of biosensors' gadgets from the "proofs-of-concept to device engineering" (Siontorou & Georgopoulos, 2021, p. 4). The biosensors market has been gathering efforts to produce more mobile health device solutions. These technologies are currently available to the more skilled sectors of the population. Nonetheless, the main goal of portable biosensors is to provide civil society with democratic biosensing gadgets, such as smartwatches, that allow for easy reading of the output towards a more accessible screening of the results, which could be complemented by an audio recording or a video of a health professional offering counselling to the patient to deal with the results (Russel & de la Rica, 2018).

The focus on the health-related advantages of nanotechnology has been the aim of various research studies that also shed light on the trendiest topics in the field literature, particularly in the context of the Covid-10 outbreak. (Choi, 2020). The rapid diagnosis and accessibility of readable information led to mass commercialisation and fast adaptation of biosensors to diagnosis gadgets, resulting in intense scientific production and proliferation of investment in the transducer areas that looked at nanotechnology as a practical response (Mobed & Shafigh, 2021; Rasmi et al., 2021).

Nonetheless, the optimistic approach that most of the literature took on the biosensors' contribution to tame the pandemic also entails new challenges. Firstly, the PCR tests used for Covid-19 diagnosis are less accurate and cost-effective than other biosensing solutions (Liu & Wachsmann-Hogiu, 2022). Moreover, the urgency to produce and spread PCR tests prevented the stable development of other biosensing models, such as the mechanical biosensors, which were not sufficiently studied and applied during the pandemic years.

The challenges, future forecasts and practical applications of biosensors in the health sector have been summarised in bibliometric analysis for the most diverse usages of this technology. A bibliometric analysis of the scientific literature production on the diagnostics of Alzheimer's (Li et al., 2023), its application in autoimmune diseases (He et al., 2023) or the prevention of cardiovascular diseases (Zheng et al., 2022) are only some of the examples that emphasise the growth of biosensors literature in the health sector and add complexity to the different possible applications in the field.

This biotechnology focuses on the supply of medical point-of-care solutions, and its usage is also forecasted for other sectors. It is possible to find literature on the application of this technology in the monitoring and evaluation of wastewater treatment (Jiang, 2018) for the detection of pathogens and toxins (Jeon et al., 2022) to ensure an effective agribusiness model (Puerta et al., 2012) and in a broader chemical engineering dimension (Gomes et al., 2019), in which the main discussion is the sensitivity level of the biosensor compounds.

The technology studies field is an ever-evolving scientific niche. It is hard to keep track of all the latest innovations in a given sector of activity. The biosensing technologies have research teams worldwide putting effort into leading the field to concrete steps towards massifying its production and utilisation (Siontorou & Batzias, 2010). The most cutting-edge developments concerning this technology follow the guidelines to initiate the commercialisation of multiplex biosensors. This will revolutionise the markets influenced by its trading and the competencies needed to develop such devices (Korniejenko, 2021).

Following Huang et al. (2009), network maps built around the fields affected by the growth of nanosensors worldwide suggest that since the last decade the areas of activity that had more potential to be influenced by the biosensors were chemistry, biomedical science and cognitive sciences. Nonetheless, semiconductors' role is starting to focus more on the most pressing challenges of the communities' futures. The environmental phenomenon has emerged as one of the most notorious dimensions in the recent history of biosensors. Therefore, there has been an effort to align the technology industry priorities to mitigate ecological degradation; these can be revealed by applying semiconductors to the agribusiness and environmental monitoring markets.

International institutions actively promote sustainability, research development, and innovation, fostering synergies between research centres and scientists from different geographical markets. Diplomatic efforts aim to enhance knowledge transfer and production methods between hegemonic poles of technology enhancement. An example is the scientific partnership between China and the United States, which have collaborated on developing Nanotechnology (Tang & Shapira, 2011).

Despite the collaboration between countries with a high volume of scientific and industrial production, the competitiveness of the nanotechnology field turns the study of biosensors heavily dependent on the geographical constraints of the markets and respective spheres of influence. Consequently, there is a branch of literature that focuses on bibliometric analysis of the production of nanotechnology at the national level. In Eastern Europe, there is a state-of-the-art influence by the share of the nanotechnology market owned by Russia or tied to Russia's dominance in that area (Lavrik et al., 2015; Terekhov, 2017; Rosca et al., 2020).

The extensive literature on biosensors in such broad areas of activity sheds light on the indefinite circumstances of this technology in the global market. Therefore, several challenges lie ahead; some are already diagnosed, such as the time-consuming activity of building stability in new biosensors, and the economic performance of the biosensor market in different geographical markets. Ethical issues also arise with the spreading of medical information through biosensors, potentially jeopardising the mass employment of big data in healthcare. To tackle these issues, the interdisciplinarity between Natural Sciences and the Social Sciences and Humanities (SSH) can play a decisive role (Holm et al., 2013); therefore, it is crucial that the SSH becomes more involved in the scientific and technological production to bridge the gap of understanding between the development of technology and the societal challenges that it can pose.

3. Exploratory Biosensors Market Analysis

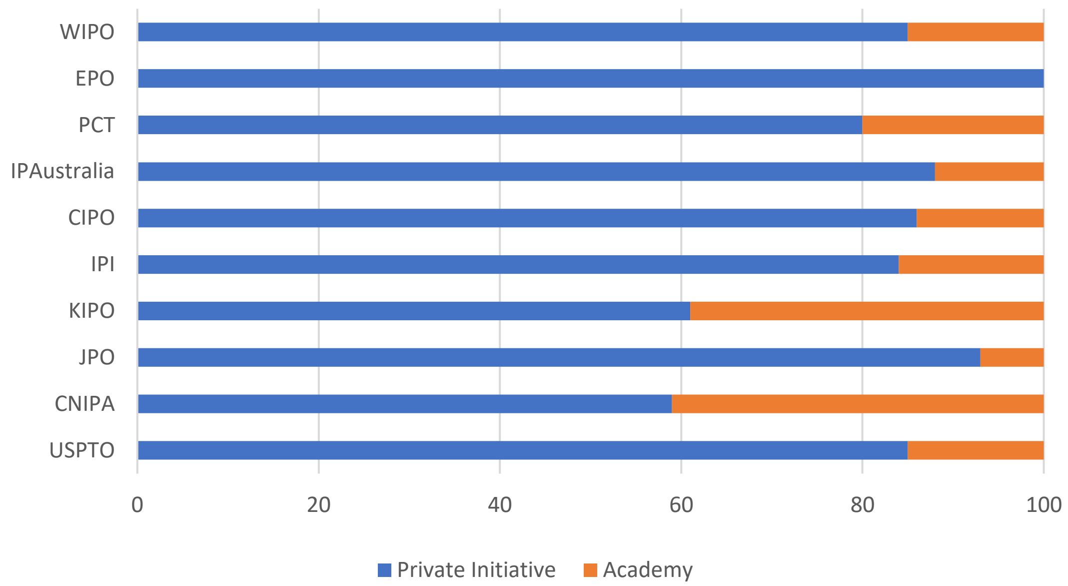
3.1 A biosensors' market overview

Following a section highlighting the role of partnerships in the biosensors field, the current section aims to discuss the current state of the biosensors market by geographical location and area of activity. This chapter will discuss the increasing number of patents and publications related to biosensor technology and the shift of markets towards new biosensor production methods.

The most crucial developments in biosensing technology in Asia have been at the front line of crucial developments in biosensing technology; the partnership between Chinese universities and the Chinese/Taiwanese industries has been prolific to guarantee sensor market patents (Figure 2). This evolution of the Chinese industry was also followed by a growth in the literature about biosensing between 2005 and 2020, as part of the National Medium to Long-term Plan for the Development of Science and Technology (Cagnani et al., 2022). This plan brought several national and international stakeholders to grow interested in the Asian industry.

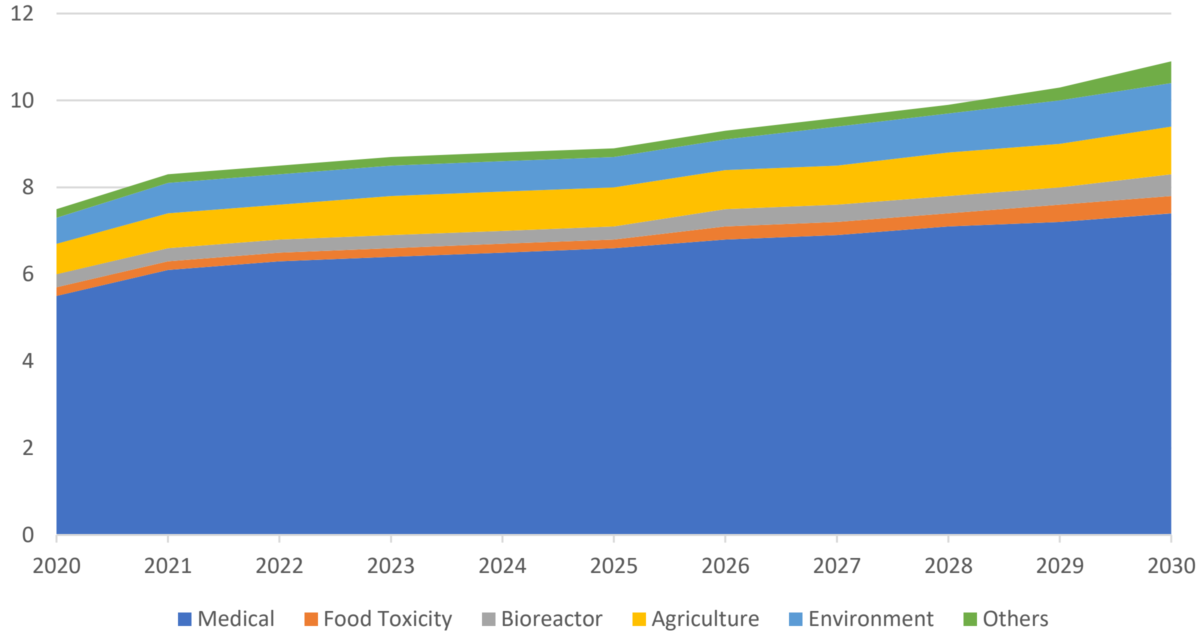
The USA tries to reach the production levels of Asian companies, placing it second in the global biosensor market. The private sector leverages USA innovation in the field, with macro-scale companies' leaders in the microelectromechanical sensors (MEMS) suppliers' realm, such as Abbott Laboratories, Endress+Hauser and Johnson & Johnson. However, it is worth noting that despite being intricately connected to pharmaceutical and healthcare activities, the biosensor market experiences varying levels of financial success. When comparing the different industries' Compound Annual Growth Rates, the biosensor market is expanding at 7,9% for 2019-2028; simultaneously, the global pharmaceutical manufacturing market (Figure 3) is expected to grow 13,7% until the end of the decade (Cagnani et al., 2022).

Figure 2. Business and Academic Patents in different Databases worldwide (1976 to 2022)



Source: Own elaboration based on Cagnani et al. (2022) with data from WIPO – World Intellectual Property Organization / EPO - European Patent Office / PCT – Patent Cooperation Treaty / IP Australia - Intellectual Property Australia / CIPO – Canadian Intellectual Property Office / IPI – Intellectual Property Institute / KIPO – Korean Intellectual Property Office / JPO – Japan Patent Office / CNIPA – China National Intellectual Property Administration / USPTO – United States Patent and Trademark Office

Figure 3. United States Biosensors market projections 2030, by field of activity (in percentage)



Source: Own elaboration based on the GVE – Global Biosensors Market Size Analysis & Growth Report 2030

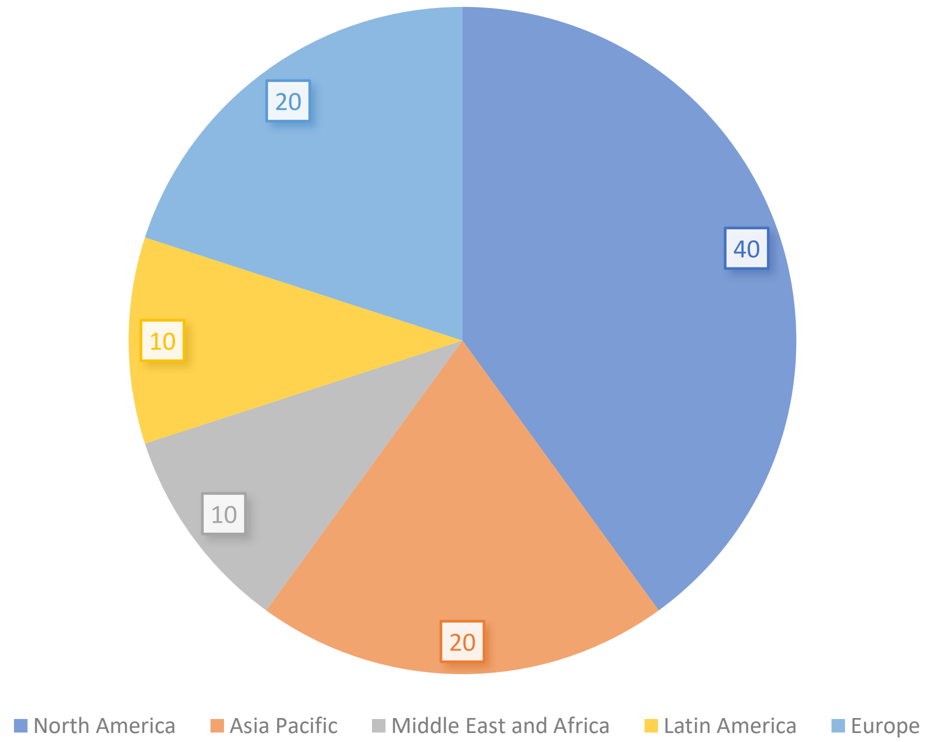
The Chinese market has also experienced growth in the technological patenting market by diversifying partnerships and penetration into different European markets. Chinese companies adopt a strategy of filing patent applications with the European Patent Office (EPO) to protect their inventions, later validating them in respective European countries. The "Annual Report 2018 – Statistics at a glance" demonstrates a growing trend of Chinese patent applications filed before the EPO between 2000 and 2018, with a tendency to keep rising. These results are highly influenced by the investment by China in its National Patent Office, which was also complemented by steady funding of the human resources that deal with the patents databases (Hsu et al., 2021).

However, China's investment in lithography has a structural problem regarding the few chipmaker suppliers, resulting in a dependence on foreign suppliers for lithography machine production. To contain the Chinese advancements in the lithography field, the USA has implemented extraterritorial restrictions through the Foreign Direct Product Rule to block the products produced outside with larger shares of USA origin technology. Despite global developments in the semiconductor markets, there is a generalized concern about the possibility of reaching the theoretical limits of the technology soon due to the reduced size of the chip being hard to replicate through lithography.

In Europe, the third largest market for the production and commercialization of biosensors (Figure 4), there is an urgency to bridge the gap between the industrial world and academic activity to stimulate sustainability in the biosensing domain. Universities in Germany, the

United Kingdom and Italy have tried to keep up with the innovation in the field. Projects such as CARE-MAN: Healthcare by biosensor measurements and networking, by the University of Tübingen, the implementation of a Centre for Biosensors, Bioelectronics and Biodevices at the University of Bath or the achievement of a biosensor patent for detection of viral particles, in the Polytechnic University of Delle Marche has promoted the biosensing industry in Europe. However, the biosensor's theoretical foundations lack practical application in the European Union industry due to bottlenecks preventing universities and industries from working together.

Figure 4. Biosensors Market Size by Region, 2021 (in percentage)



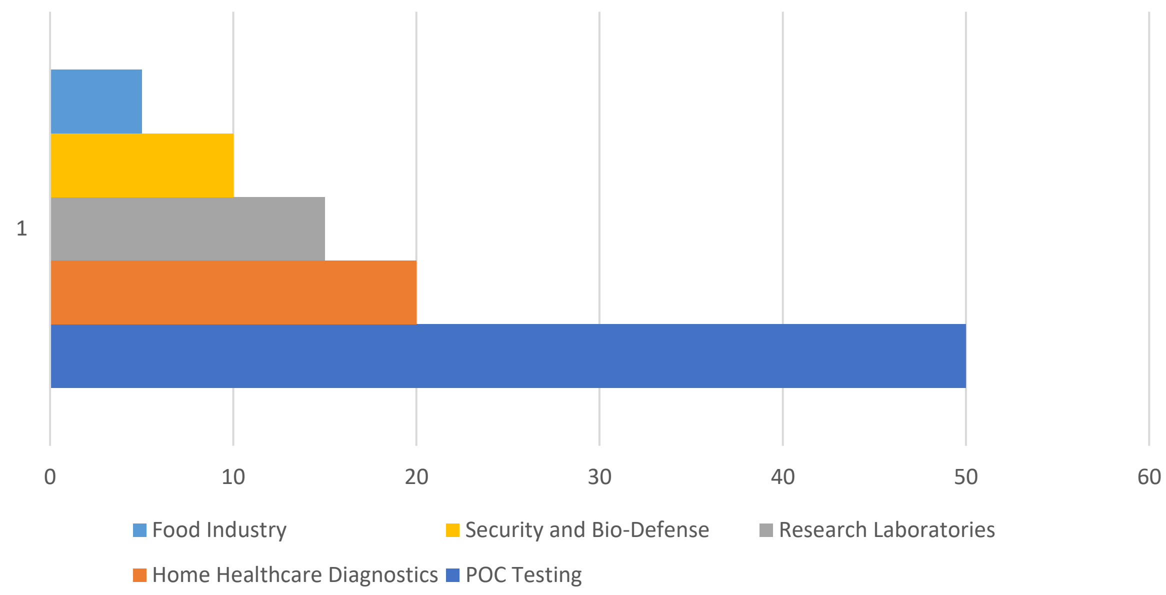
Source: Own elaboration based on the Precedence Research - Biosensors Market Size, Growth, Trends, Report 2022 to 2030

It is hard to explain where the obstacles to implementing this technology are. Nonetheless, it is known that universities in Europe have been integrating more researchers at their biotechnology centres with a solid capacity to adapt to exogenous knowledge and produce new expertise (Siontorou & Batzias, 2014). This process of prolific knowledge acquisition does not reflect the sparse numbers of biosensors commercialization in the industrial market (Luong. et al., 2008). Research dynamics about a disruptive technology such as biosensing can be a critical barrier to its commercialization, as highlighted by Siontorou and Batzias (2014).

The non-commercial focus of university research, which prioritizes exploring the scientific aspects of the technology rather than revenue generation, acts as a bottleneck to the commercialization of biosensors. This poses complex challenges to transmitting knowledge about biosensors from academia to the industrial market.

Furthermore, the innovation of wearable medical biosensors has recently revolutionized the market, promoting comfort and practicality in the patient's diagnosis (Ye et al., 2020). In the food quality evaluation, the path drawn by the biosensors industry is to keep the tendency of lowering the prices for food processing and quality control. This has been exemplified by the nano enzyme artificial biosensors, which are produced at a lower price than the devices using conventional natural enzymes (Wang & Gunasekaran, 2020). The most regular usage is based on detecting ions, pesticides and biological contaminants (Muenchen et al., 2016; Sohrabi et al., 2021). Nevertheless, new applications have been found (Figure 5), including tracking antibiotics in the food chain (Majdinasab et al., 2020).

Figure 5. Biosensors Market Share by end user, 2021 (in percentage)[1]



Source: Own elaboration based on the Precedence Research - Biosensors Market Size, Growth, Trends, Report 2022 to 2030

The type of technology can vary from nanoparticle-based sensors, nanotube-based sensors or nanowire-based sensors. The nanoparticle-based sensors are primarily used in healthcare Point-of-care POC devices; the extracellular detection ability of this technology typology is helpful for early tumour diagnosis (Martín-Garcia et al., 2020). The nanotube-based biosensors are

[1] POC Testing – Point-of-Care Testing

chemo-resistive sensors that employ a multiplex analysis. This technology faces challenges such as the integration into low-power small devices, which can be particularly helpful in extending the battery of these devices (Tang et al., 2017). The nanowire-based sensors' composition is adequate and accurate in its measurements due to the electrical controllability provided by its materials (Wang et al., 2016).

The typology of nano biosensors products is split into wearable and non-wearable. As mentioned earlier, developing wearable devices is one of the innovation priorities for biosensor manufacturers. Wearable biosensors represent a significant advancement in healthcare diagnosis and can also track various physical parameters relevant to high-performance athletes (Ray, 2019). These devices offer a level of comfort that continues to improve as the technology becomes more accurate and miniaturised.

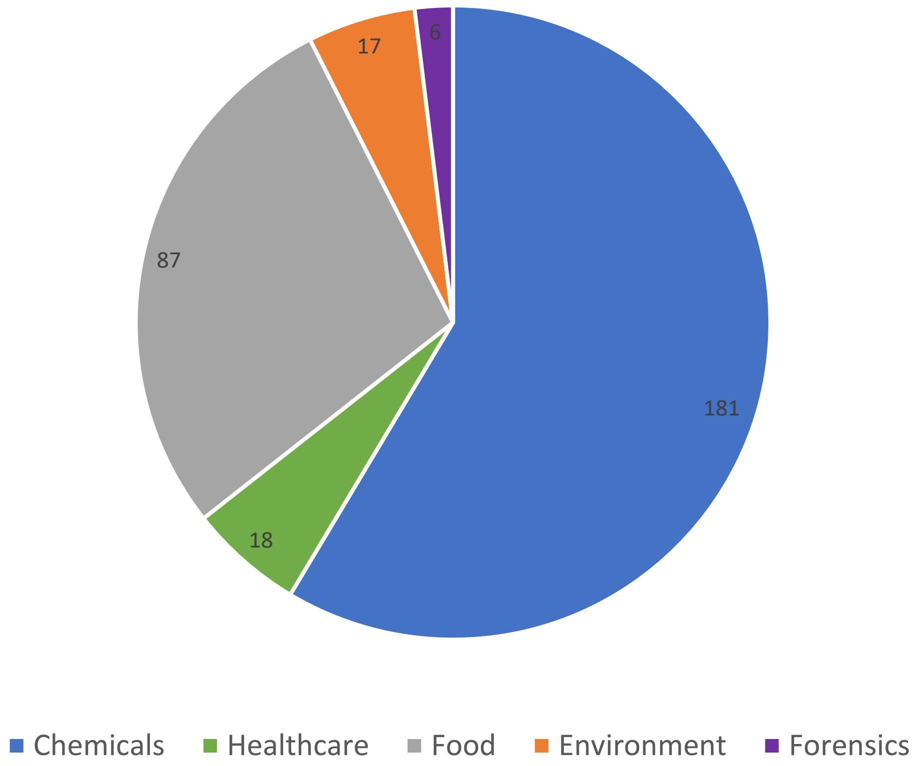
On the other hand, non-wearable biosensors are challenged to accompany the strong presence of the current wearable devices in the nanotechnology market. Therefore, the non-wearable biosensors, which were the pioneer typology in this case, have tried to keep up with the rhythm of the wearable biosensors by engaging with the networks facilitated by the Internet of Things (IoT) (Karthick et al., 2020). The wireless interconnection between devices and the big data stream of information permits an in-depth knowledge of its users. Therefore, there is a need to create a framework of action between the technology users, the entities that own the data and those providing the service. The users must have more information about biosensors at their disposal before engaging with the MEMS. The entities and professionals with access to the data should build a platform for data sharing that complies with the regulations and ethical requirements concerning data privacy. The companies that provide the service are responsible for ensuring that data leakages are rare and that there is a shared protocol for data protection. The large number of devices that collect private information, especially regarding healthcare, require a public policy to establish the limits of data utilisation for the users, the data owners and the service providers (Zhang et al., 2021).

An exploratory analysis of the European Patent Office database was developed to understand the extent to which the different geographical markets are producing intellectual property/patents in the fields of activity where biosensors have been actively implemented in the last decades. The keyword biosensors* was combined with the area of activity (e.g: *Chemical; *Healthcare) and filtered through the geographical location (e.g: *China, *USA, *Europe) to comprehend the divergences between markets.

3.2 Chemical industry

The chemical industry has a unique relationship with biosensors, as they play a fundamental role in all production phases rather than being end products themselves (Figure 6). Some examples concern the usage of photolithography to build microstructures during the manufacturing process or the utilization of graphene to act as a receptor in the transducer.

Figure 6. Number of Articles by Industry, February 2023 (WoS)



Source: Own elaboration based on WoS data (2023)

The European Patent Office database reflects the diversity of segments in the chemical industry and market that can be positively affected by the biosensors' mass production. A total of thirty-nine thousand one hundred and sixty-one (39,161) registered results are found by crossing the keywords Biosensors and Chemical. The number of patents involved in releasing innovative biosensing gadgets in the chemical industry is dominated by the keywords USA, revealing the peak performance of the USA in this market.

Interestingly, Germany ranks second with four thousand three hundred and thirty-seven (4,337) registered patents, which seems paradoxical considering the lower quantity of patents including the keyword Europe (813). There is an underdevelopment of the European regions compared with the USA, except Germany and, in some cases, the UK or Nordic countries, concerning the patents listed in the European Patent Office database. When filtered by words, the third most mentioned geographical market is China, with two thousand six hundred and eight (2,608) entries.

The literature does not corroborate the patents' patterns. A considerable number of publications on biosensing devices are released by the Asian market, which has top-notch facilities to evolve the necessary nanotechnology. Simultaneously, the USA is relegated to the second plan when discussing the state-of-the-art's depth. There are cleavages between the practical application of biosensor production and the patents analysis with the literature in the field.

There is a more accentuated participation of the academic realm in the biosensing industry in the Asian market compared with the western forms of production. The one hundred eighty-one (181) articles were collected in total by simultaneously filtering the keywords biosensors and chemicals in the WoS database until February 2023. The presence of silicon in the biosensing chips is highly referenced (Park et al., 2007; Peled et al., 2014; Lo Faro et al., 2022) due to the large size of the surface area and the optical properties that allow for easy reading of the results (Vercauteren et al., 2021).

The future forecasting for this technology includes the mass commercialization of luminescent Silicon nanowires that reinforce the sensitivity when detecting pathogen genomes without PCR amplification (Lo Faro, 2022). Other state-of-the-art main lines include the use of graphene for cancer detection biomarkers (Govindasamy, 2022), the optimization of graphene biosensors as translated into further development in the fields of direct electrochemistry of enzymes, electrochemical detection of small molecules and in the immobilization of these biomolecules to graphene functionalized surfaces (Celik et al., 2015).

In addition, new synthetic methods are rapidly expanding the types of chemical compounds employed to modulate a broader spectrum of biological targets, leading to changes in drug discovery techniques (Campos et al., 2019).

3.3 Healthcare

The healthcare market has witnessed exponential growth in the application of biosensing devices, driven by factors such as the Covid-19 pandemic and the reinforcement of point-of-care technology to a quick. Crossing the keywords *biosensors and *healthcare in the European Patent Office, five thousand eight hundred and seventeen (5,817) results were retrieved, with the majority being related to the keyword US with three thousand two hundred and five mentions (3,205). A smaller portion of the healthcare patents filter search has been distributed as follows – Germany with thousand and sixty-five (1,065) patents, China with four hundred and fifty-seven (457) and Europe registered two hundred seventy-four (274) results. It is worth noting that patents may appear under multiple geographical keywords as the search filters are not exclusive categories.

The literature in the field is still lacking further depth; however, from the eighteen articles (18) that resulted from the usage of the keywords *biosensors and *healthcare, the spectrum of application is mainly framed by the possibilities of biosensing devices to engage with the internet of things (Maghawry & Ghoniemy, 2019; Ahmed & Kannan, 2022; Aledhari et al., 2022) and the big data through wireless gadgets (Navya & Deepalakshmi, 2018).

The prospect of combining the regular monitoring of health-related levels such as sweat glucose (Zhao et al., 2019), blood test modules (Guo et al., 2021) or saliva (Zarrin et al., 2020) with the cyber potential of wearable devices creates room for a new market of health tracking that raises new challenges for industrial production (Vashist, 2012). New paths are being drafted through the energy optimization of these devices (Saba et al., 2020; Su et al., 2020) and the auto-sufficiency of its batteries. The elaboration of biosensors combined with the digitalization of personal data opens new challenges concerning the data management and ethical procedures of health information which have not yet been comprehensively addressed (Mishra & Agrawal, 2019).

In the pharmaceutical industry, chemical synthesis plays an essential role in researching and developing new medicines. Campos et al. (2019) reviewed some of the advantages of recent innovations in synthetic methods. The authors emphasize two aspects: small-molecule catalysts stimulated by visible light and enzymes engineered to be versatile beyond what they are designed to do and bio-orthogonal reactions that selectively modify proteins for conjugation.

Nowadays, biosensors are essential for diagnosing viruses due to their higher advantages; the genomes of different viruses can recombine to form new progeny, making it difficult to detect using only one biomarker. Thus, a smart design of a multiplex biosensor platform is crucial for concurrently detecting multiple analytes and improving diagnostic accuracy.

3.4 Food safety

The food safety and food fraud markets have a significant number of registered patents, with twelve thousand eight hundred and fifty-eight (12,858) entries at the European Patent Office. The distribution of keywords filters follows a similar pattern to other dimensions. The US dominated the patents references with four thousand nine hundred and four (4,904) registered references, followed by Germany (1,597) and China (1,305). The keyword *Europe was the least mentioned, with four hundred and sixty-two (462) mentions. The analyses of pesticide molecules and fertilizers present in agricultural activity contribute significantly to this market's growth (Ramachandran et al., 2022), driven by initiatives from organizations like the World Health Organization (WHO) to promote sanitary regulations and tight legislation on commercialized food.

From the eighty-seven (87) articles related to food safety found on the WoS database, most of them use an analytical method based on enzymes applied to detect several possible features such as glucose, fructose, lactose or amino-acids in food (Monosik et al., 2012; Basso & Serban, 2020; Nadaroglu & Alayli; 2020; Ahangari et al., 2021).

Pathogen detection is also a frequent topic in this biosensor industry for food safety. The typology of biosensors applied in pathogen detection is not only based on enzymes. There is a multiplicity of food-quality biosensors (Cho et al., 2014). The typology of the biosensor used is heavily dependent on the sample size and type. For example, to analyse nucleic acids, the most conventional methods are microfluidic PCR biosensing devices (Cho et al., 2014).

On the other hand, the evaluation of the protein is supported mainly by technology such as optofluidic biosensors and nanoparticle methods. The detection of bacteria and similar agents in food is an essential application of biosensors in the agriculture sector. This focus on infectious agents contributes to expanding the spectrum of biosensor applications in the food market (Alloush et al., 2006; Grossi et al., 2009). Biosensors are also used to track and quantify bacterial aggregation, enabling better understanding and control of bacteria in food and beverages (Grossi et al., 2009).

3.5 Environmental Monitoring

Concerning the environmental mentions in the biosensors market, the European Patent Office registered twenty-seven thousand five hundred and fourteen entries (27,514). In this industry, once again, the USA dominated the keyword references with ten thousand hundred and ten (10,110) patents mentioning the word *US. Germany has three thousand twenty-two (3,022) mentions, significantly more when compared with the Patents filtered by the word *Europe (654). China does not have a relevant role in this market compared with other industries; the two thousand-one (2,001) patents filtered by the keyword *China are illustrative of the paucity of Chinese patents in this field.

The literature on environmental monitoring and biosensors is limited; the seventeen (17) articles filtered in the WoS database by the keywords *biosensors and *environment are mainly dedicated to issues related to monitoring environmental settings, particularly in aquatic environments (Mills & Fones, 2012; Nandimandalam & Gude, 2019; Hideshima et al., 2022). Environmental pollution and contaminants monitoring are also a large part of the state-of-the-art in this industry (Zheng & Gong, 2003; Basu & Kovalchuk; Mohsen, Elsayed & Bazedi, 2017). The biosensing devices for environmental monitoring are decisive in tracking the pollutants in rural areas, gathering a high potential for healthier and maximized agricultural production (Tothill, 2001).

3.6 Forensics and Security

The application of biosensors in the forensics field has room to grow; hence there were two hundred seventy-three (273) patents registered in the European Patent Office when crossing the words *biosensors and *forensics. From those patents, one hundred forty-six (146) included the word US, forty-eight (48) had the filter Germany, eighteen (18) included the word China and fourteen (14) with the filter Europe. The analysis of patents' keywords reveals an underdevelopment of the Chinese forensics market compared to the previous industries analysed. On the other hand, the USA criminal justice system is actively trying to implement biosensors' diverse applications in its judicial activity, with more than half of the patents registered mentioning the word US.

The extensive array of application domains turns biosensing into a fundamental technology for developing the judicial field in cases that need the detection of alcohol, drugs, or gunshot residues (Yáñez-Sedeño et al., 2019). However, introducing new biosensing tools in the forensics market must carefully consider ethical and moral challenges, such as privacy concerns and the implications of big data analysis.

Forensics have been a peripheral market for biosensors producers in the last decades, but recently has gathered some interest derived from the ability to measure DNA components to provide new information to the authorities dealing with criminal cases. Some of the most notorious advances in this market are related to the performances achieved in the analysis of finger-marks (Wood et al., 2012), sweat, blood and alcohol.

A multiplex biosensor that could track all these dimensions would be valuable and less time-consuming than the ones utilized nowadays. Innovative developments in the field include using bacteria to detect gun residue, which can be decisive in crimes involving fire weapons (Barber et al., 2019). Besides that, the potential of wearable biosensors as a regular part of mental healthcare treatments can be directly connected with the evolution of the forensics diagnosis of mental illness; therefore, these biosensors can also be applied in the same way to establish forensics psychiatric evaluations (de Loof et al., 2021).

4. Methodology

4.1 Exploratory Bibliometric Analysis

After an extensive overview of the biosensors market, it is important to clarify how this research proceeded to an exploratory bibliometric analysis to draw maps of partnerships and comprehend what the most active competencies (evaluated through the distribution of the keywords), authors, institutions, and countries to play a role in the latest developments of the different photolithography and biosensors' related markets were.

The biosensors' growth in all markets has increased the literature in the field. A bibliometric analysis of the produced literature is required to understand the latest tendencies in the scientific development of the field. This analysis will help position the European universities and research centres when compared with the production level of other scientific locations.

4.2 Methodological Options for the Bibliometric Analysis

To conduct the bibliometric analysis, a set of keywords directly related to the sustainable production of biosensors, such as the one proposed by the BioAssembler, were used. After careful discussion between the consortium's partners, the set of keywords agreed upon were – *Photolithograph, *Transducer, *Multiplex *Biosensor, *Wafer, *Microchip, *DNA Hybrid, *Synthetic Chemistry, *Liquid Analyte, *Silicon biosensor and *Microelectromechanical Sensor. These keywords were searched as topics on the Web of Science database, with complementary filters that could add to the relevant results. Those filters included only the 'Science Citation Indexed Expanded' and the 'Emerging Sources Citation Index' articles, notes and reviews indexed and published in the last five years (2018-2023).

The most common criteria to define a network analysis of the scientific evolution of any innovation field are the most published and cited authors, the most common keywords and the countries/organizations that publish and are more mentioned in the literature (Rueda et al., 2007; Caldera & Debande, 2010). The keywords were vastly tested on the Web of Science using the Boolean operators "and"/"or" to build a body of literature that accurately portrays the state-of-the-art in the biosensors production field. The results of the bibliometric analysis will be presented and discussed in the following sections.

5. Web of Science Bibliometric Analysis Results

5.1 Keywords

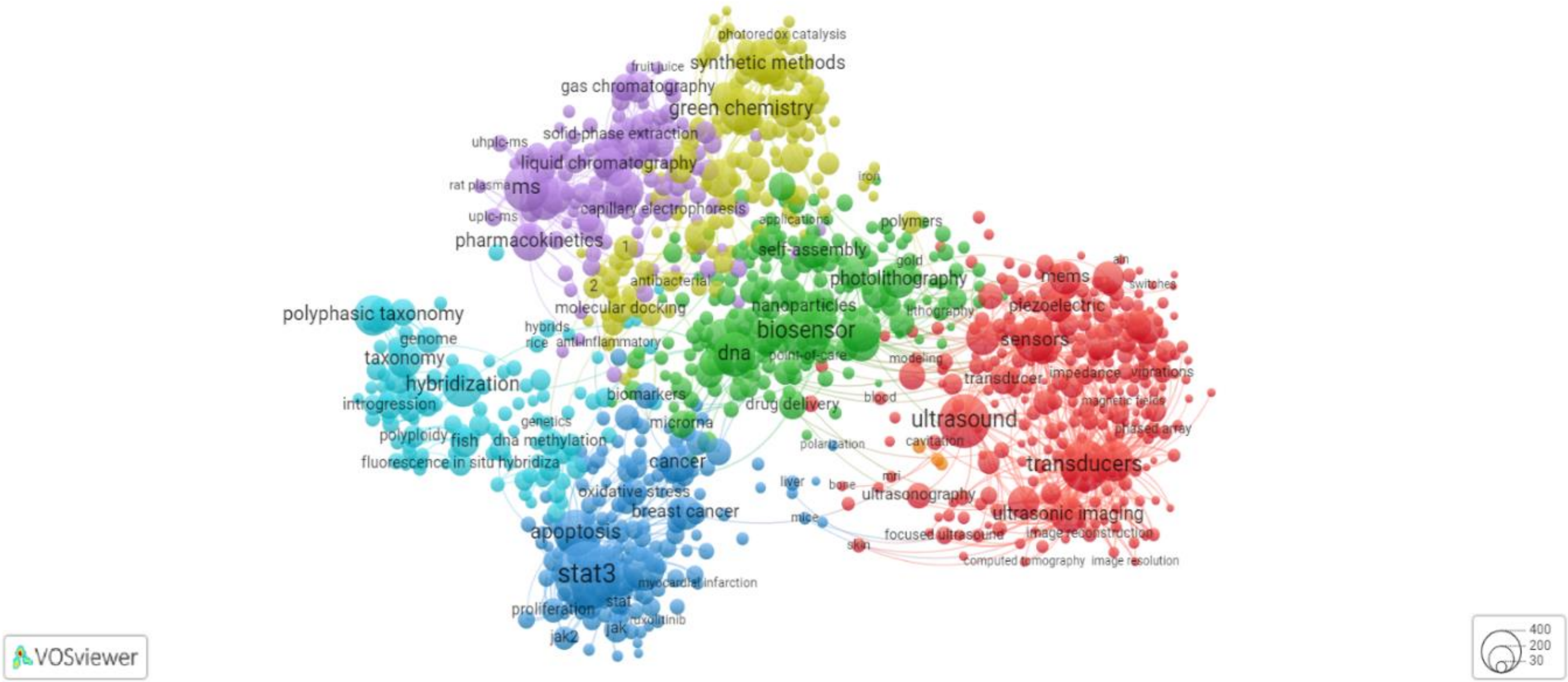
Author keywords

The analyses of more than eighty thousand results for the author keywords resulted in a wide dispersion of the fields of activity. The author keywords are chosen by the researchers that publish their scientific work to highlight the most discussed topics in its work. By the network analysis, six agglomerates of keywords can be found – firstly, the biosensor group, comprising words such as photolithography, DNA, nanoparticles and self-assembly (in green in Figure 7). This group occupies a place in the centre of the network by having synergies with all the remaining groups. Connected to the biosensor group are four clusters of similar dimensions and relevance.

In yellow (Figure 7), the green chemistry and synthetic methods bridge the biosensor group with the agglomerate of liquid chromatography and pharmacokinetics. From these relations of relevance, it is possible to look at green chemistry as an intermediate between the biosensors' central group and the possibility of applying it for pharmaceutical purposes. The two groups in blue, have a more peripheral relation with the central agglomerate. However, emphasize the importance of health-related topics for the literature in the field. Keywords such as *hybridization, *stat3, *polyphasic taxonomy and *breast cancer are some of the most notorious in these two groups. There is an implicit link between these two groups, more concerned with the functioning of the human body and its components, with the central biosensor group.

The largest and more dispersed group is the transducer category (red; Figure 7). This group has little connections with the other groups, as it covers issues in the domain of the usage of biosensing devices. Therefore, the most relevant words in this group are *transducer, *ultrasound, *ultrasonic image, and *sensors.

Figure 7. Network Distribution by Authors' Keywords



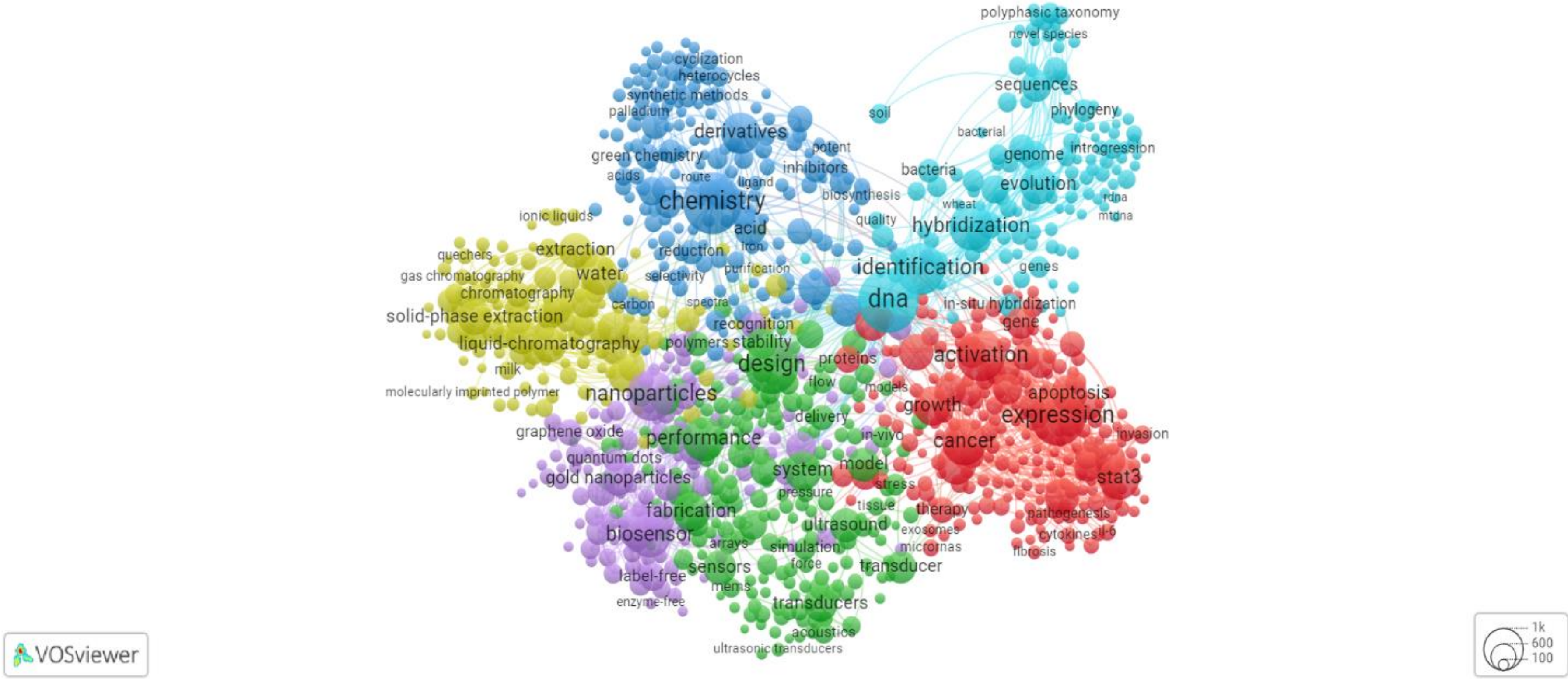
Source: Own elaboration using VOSviewer based on WoS data

Keywords

For the same publications analysed in the section above, the keywords selected by WoS have a more homogeneous distribution when compared with the author's keywords (Figure 8). This map keeps the same six groups as the author's keywords, although it has stronger links between them when compared with the previous map. Notably, the word *transducer has lost some of its importance in this dimension and has become more peripheral, while the centre of the network is now filled by terms such as design and performance (Figure 8). This replacement of keywords can be explained by the natural evolution of the technology, which seeks to build biosensors that provide faster and more reliable results with reduced sizes to maximize the levels of comfort and portability. The words that fall in the centre of the map and the centre of the green group highlight the sensor usage components as fundamental to the literature in the field.

All the areas of activity that can influence and be influenced by the development of biosensors are built upon the design and level of performance that the sensors might achieve. New words have emerged in this network analysis, such as expression, derivatives, identification and chemistry. On the other hand, terms like polyphasic taxonomy or ultrasonic transducers were pushed to the outskirts of the map as keywords of small density.

Figure 8. Network Distribution by Keywords



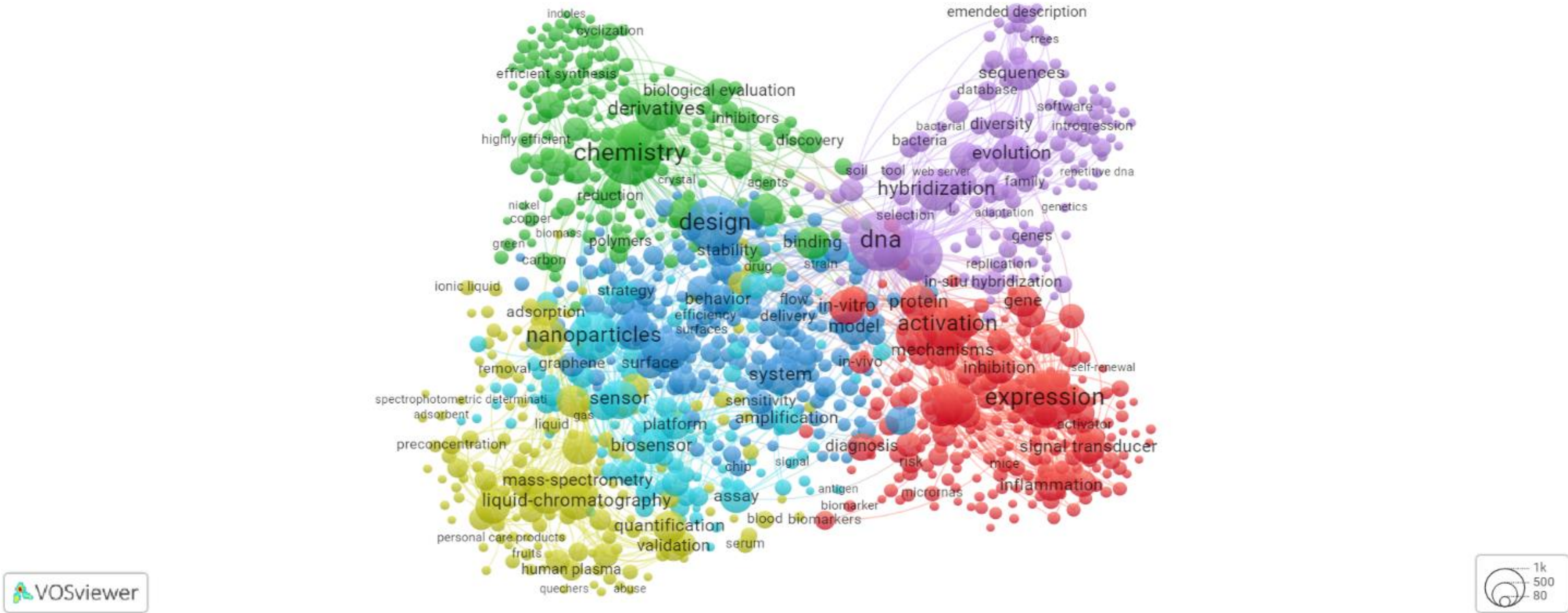
Source: Own elaboration using VOSviewer based on WoS data

Keywords plus

The keywords plus network, generated by an algorithm, yields similar results to the ones found in the keywords network (Figure 9). Once again, we can observe six diverse groups of words, with the same distribution as the previous map (Figure 8). The term *design can be found again very close to the centre of the map, close to words that gravitate around it in the biosensor production method, such as binding and stability (Figure 9). Some new keywords unseen in previous maps (Figures 7 and 8) have also emerged to notoriety in this network – *activation, *in vitro, *model and *behaviour. The strong presence of words such as chemistry, expression and DNA justifies the similarities between the keywords of these three maps.

In a nutshell, looking at the three network maps, the most significant keywords in the scientific literature on biosensors are: DNA, chemistry, nanoparticles and design. While the first three words can fall under the same common umbrella of the chemical industry, the fourth word (design) reveals a general state-of-the-art concern with the efficiency of the biosensors' method of production design and how the design can impact the performance of the devices.

Figure 9. Network distribution by Keywords plus



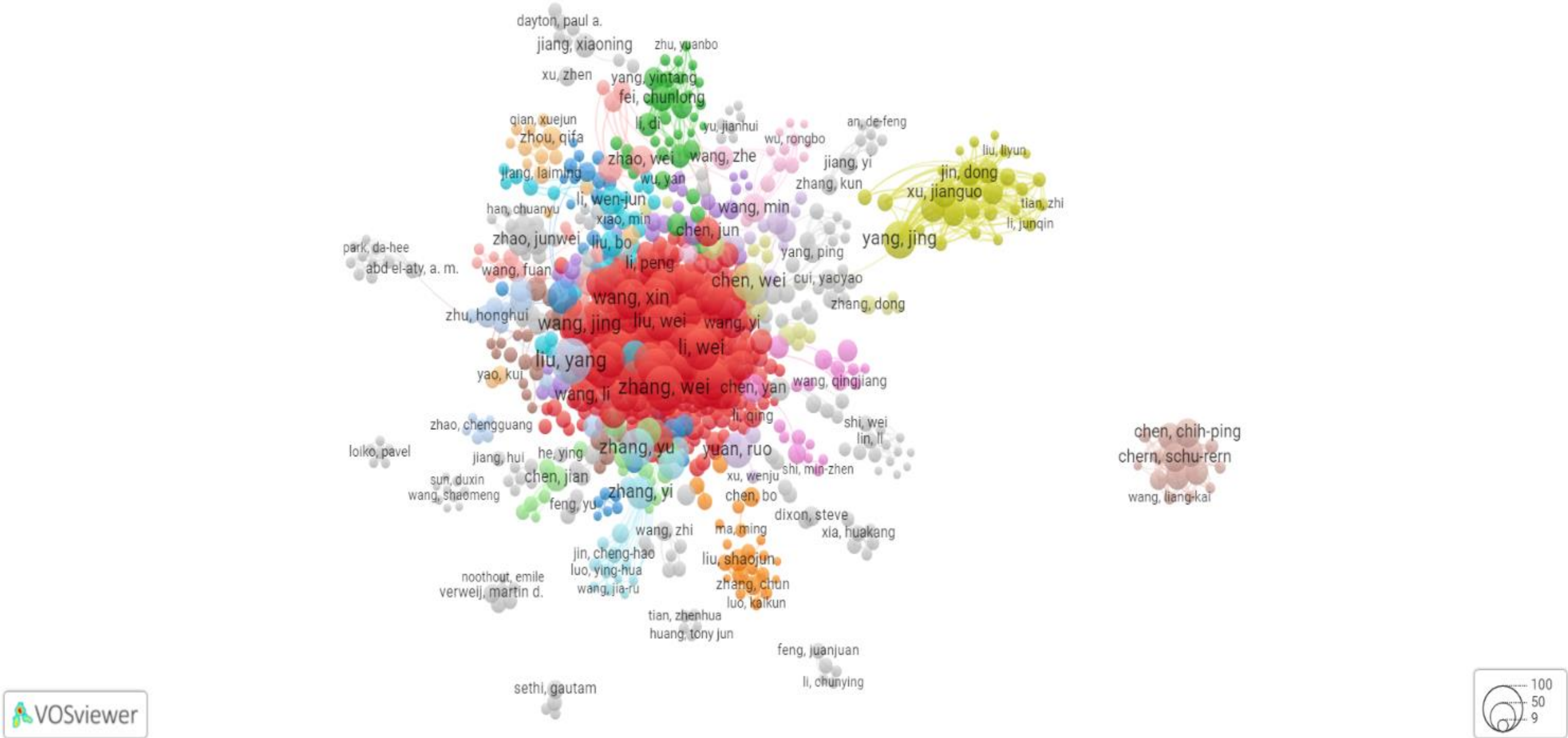
Source: Own elaboration using VOSviewer based on WoS data

Authors

Based on analysing the abovementioned keywords, the list of the most published authors deserves a deep reflection from the European scientific institutions. It is crucial to understand what has prevented authors in European institutions from being more prolific in the biosensors field, once the large majority of the thousand authors with more publications in this scientific realm are from Asian institutions, most predominantly based on Chinese institutions.

The academics in the red dots are the most notorious, with several publications emphasising the names of Wang, Xin; Zhang, Wei; Wang, Jin and Li, Wei (Figure 10). The aggregation of dots in the centre of the map exemplifies the strong link of the names mentioned above with the rest of the authors in the networks; the homogeneity in the geographical dispersion of the authors, who are mainly based at the Chinese Academy of Sciences, can justify this phenomenon.

Figure 10. Network distribution by Authors



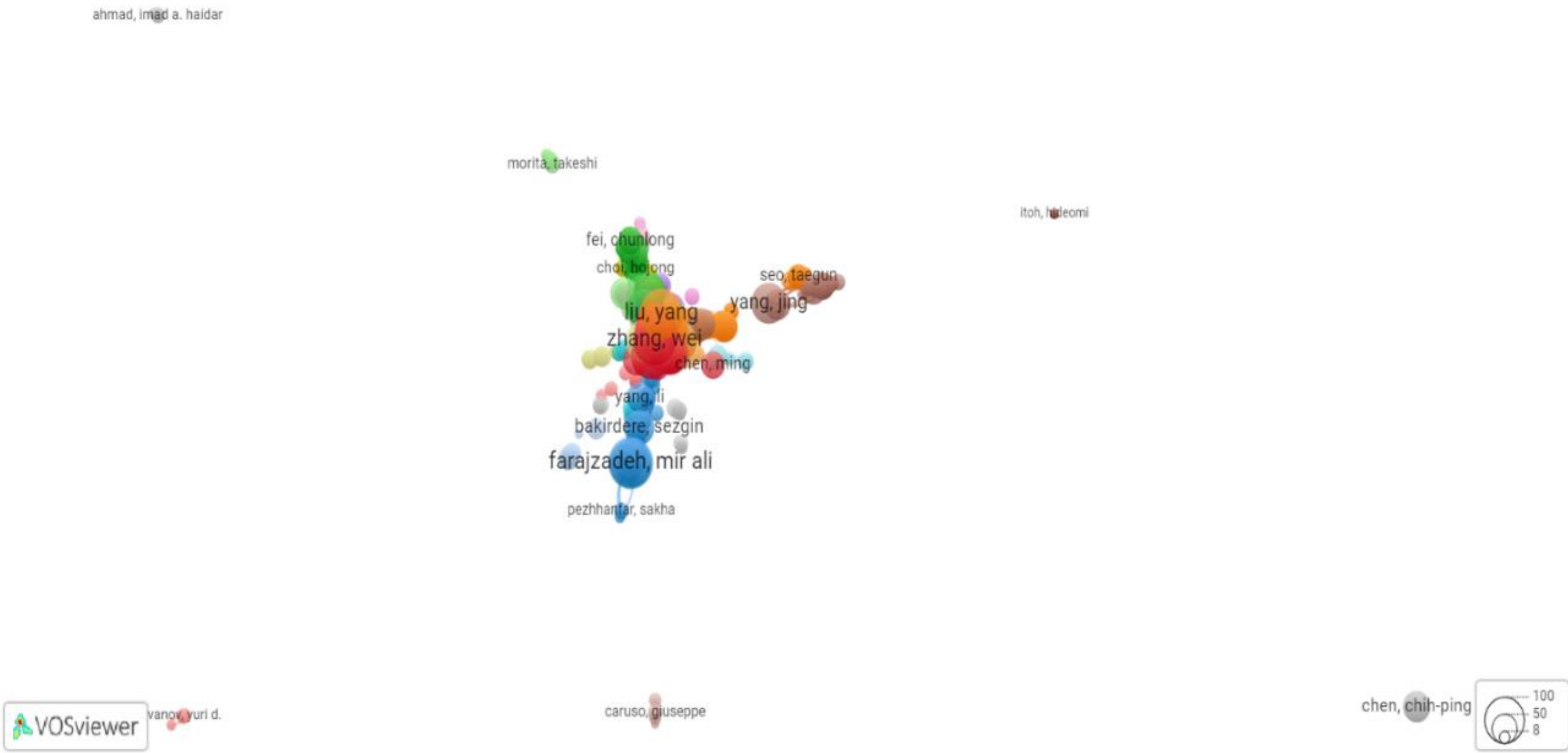
Source: Own elaboration using VOSviewer based on WoS data

Cited Authors

The network of most cited authors in the biosensors field (Figure 11) exhibits a distinct pattern compared to the most published authors' map, although Zhang, Wei is a relevant shared name between both images, occupying a central placement in the two networks. The hegemony of authors based at Chinese institutions is less noticeable than in the previous map, despite having some scholars' names in relevant positions, such as Liu, Yang and Yang, Jing; instead, those positions were occupied by authors from middle eastern universities (Figure 11).

Once again, this map corroborates the significant dominance of the Asian scientific market in the biosensors' domain, which is reserved for Chinese academics and other geographical locations in Asia, more concretely, the Asian middle east. Nonetheless, the Japanese case engrosses the complexity of this analysis, once scholars from Japanese institutions that are present in this network do not establish connections, or have weak links, with other scholars in Asia. Outside of Asia, in a more peripheral position, it is the name of Guiseppe Caruso (Figure 11), an Italian scholar based at the University of Catania and one of the most cited in the European panorama. However, it does not bridge associations with scholars from other scientific locations.

Figure 11. Network distribution by cited authors



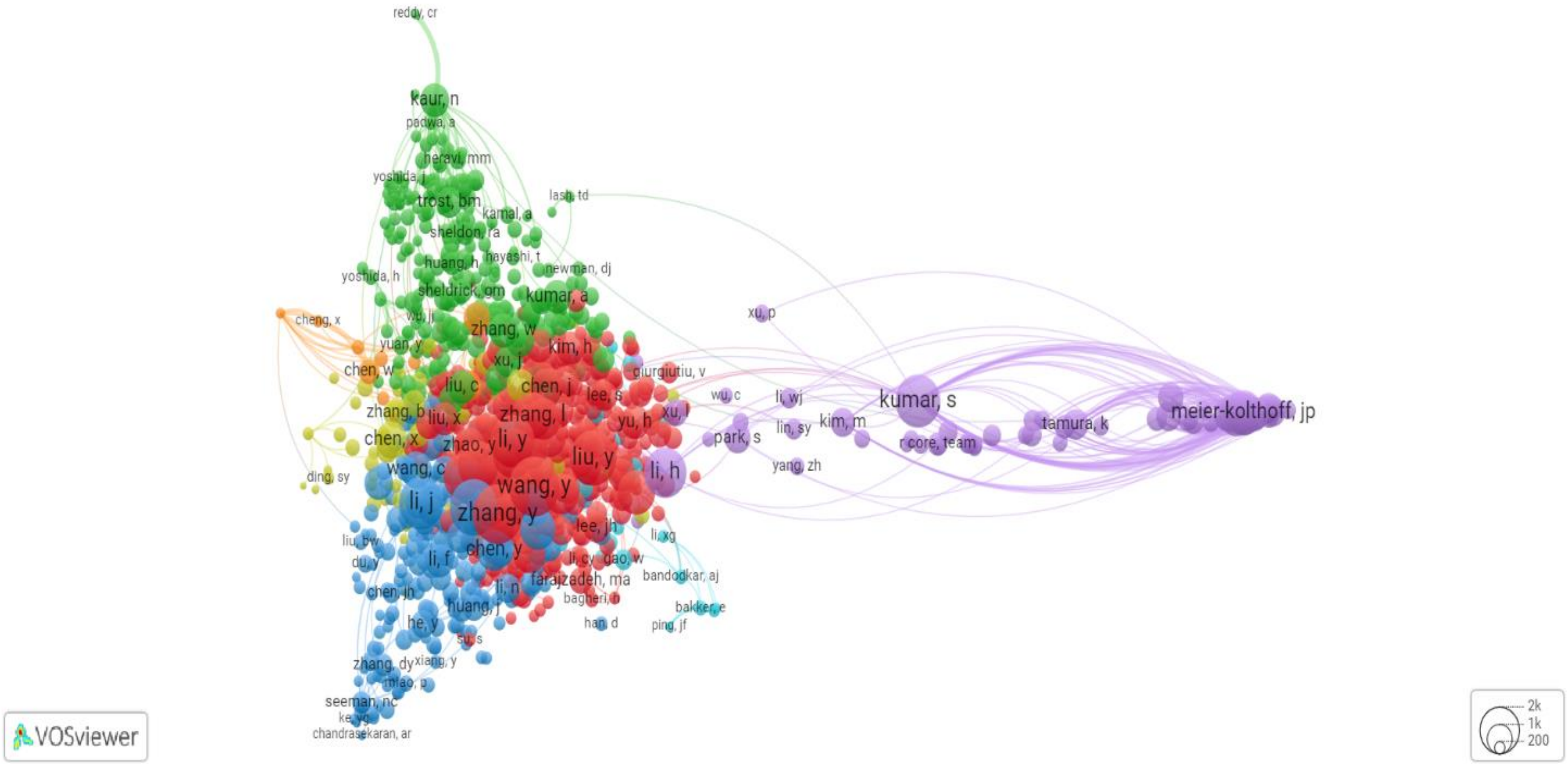
Source: Own elaboration using VOSviewer based on WoS data

Co-citation authors

The co-citation network shows an intense accumulation of authors in the red dots (Figure 12) with similar epistemological conceptions. The hegemonic position of the Chinese Academy of Sciences and other Chinese universities in the photolithography field justifies the strong position of several Chinese-based authors in the centre of the map (Figure 12), with some being so connected that gives the network a nexus of juxtaposition between the red, yellow, blue, and green central dots. Some authors can be highlighted from this aggregation of dots – Wang, Y; Zhang, Y; and Liu, Y.

There is a visible presence of other Asian-based authors (in purple; Figure 12) from South Korea, Japan, and India with weaker links to the centre. However, these co-cited authors have a fundamental role in the scientific field. They establish medium-intensity links with European scholars, such as Meier-Kolthoff, a highly cited academic and reference in the European biosensors field. Without these “bridging” authors, this network would mirror the almost total disconnection between the European and Asian biosensors markets.

Figure 12. Network distribution by co-citation authors



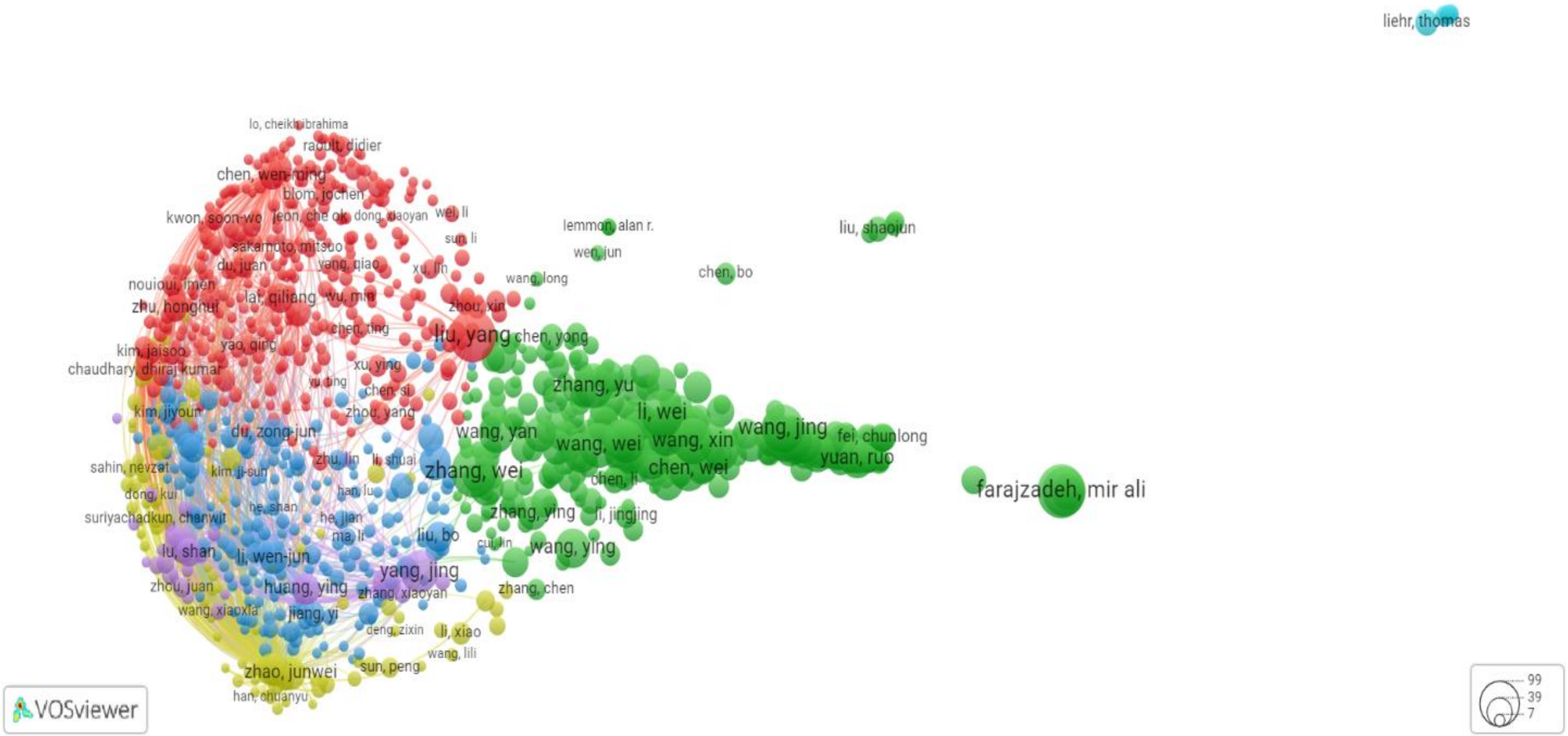
Source: Own elaboration using VOSviewer based on WoS data

Coupling authors

The coupling author citations' network is similar to the previous networks analysed in this bibliometric analysis. The predominance of Chinese-based authors in the core is once again notorious, with particular emphasis on the size of the dots of names like Wang, Xin; Wang, Wei; Zhang, Wei and Wang, Jing (Figure 13).

These authors are the centre of a coupling citations dynamic that has links with the vast majority of the authors in the network, most of them being part of different Asian research centres and universities with institutional ties between them. It is interesting to comprehend that Farajzadeh, Mir Ali, an influential author in the biosensors' field with many coupling citations, does not have any links with the Chinese scholars in this analysis.

Figure 13. Network distribution by coupling authors



Source: Own elaboration using VOSviewer based on WoS data

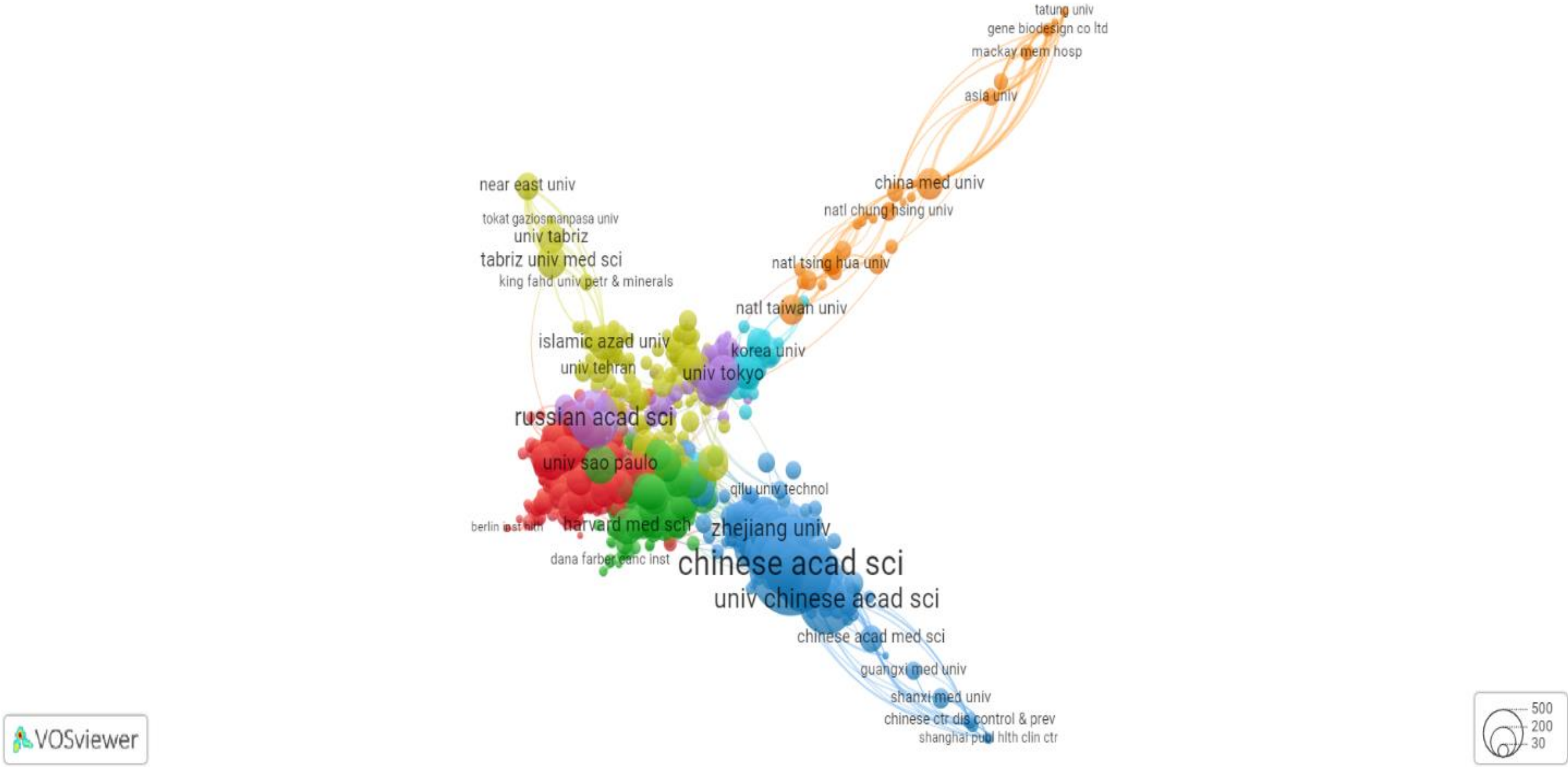
5.3 Organisations and countries

Organisations

The organisations with a more prolific track of publishing articles, notes and reviews on the biosensors field are the Chinese Academy of Sciences and the University Chinese Academy of Sciences, which are classified by different terms on the map (Figure 14), despite being the same organization. However, the Chinese Academy of Sciences is not at the centre of the map. It has different institutional dialogical connections than other institutions such as the Harvard Medical School, the University of São Paulo or even the Russian Academy of Sciences. These links imply partnerships between institutions that are revealed through co-authorships. Other universities from Asia, such as the University of Tokyo, Korea University and Zhejiang University, are also close to the core of the network analysis (Figure 14), despite not being as prolific as the Chinese Academy of Sciences in terms of publication numbers.

A considerable heterogeneity of influential organisations contributes to understanding the state-of-the-art in the biosensors field. With the apparent predominance of Asian institutions, some scientific institution clusters work autonomously, as represented by the yellow and orange dots (Figure 14). While the yellow cluster aggregates institutions from Turkey and the Middle East, the orange niche has more fundamental representatives in Taiwanese institutions and brings together organizations from Southeast Asia and Oceania.

Figure 14. Network distribution by Organisations



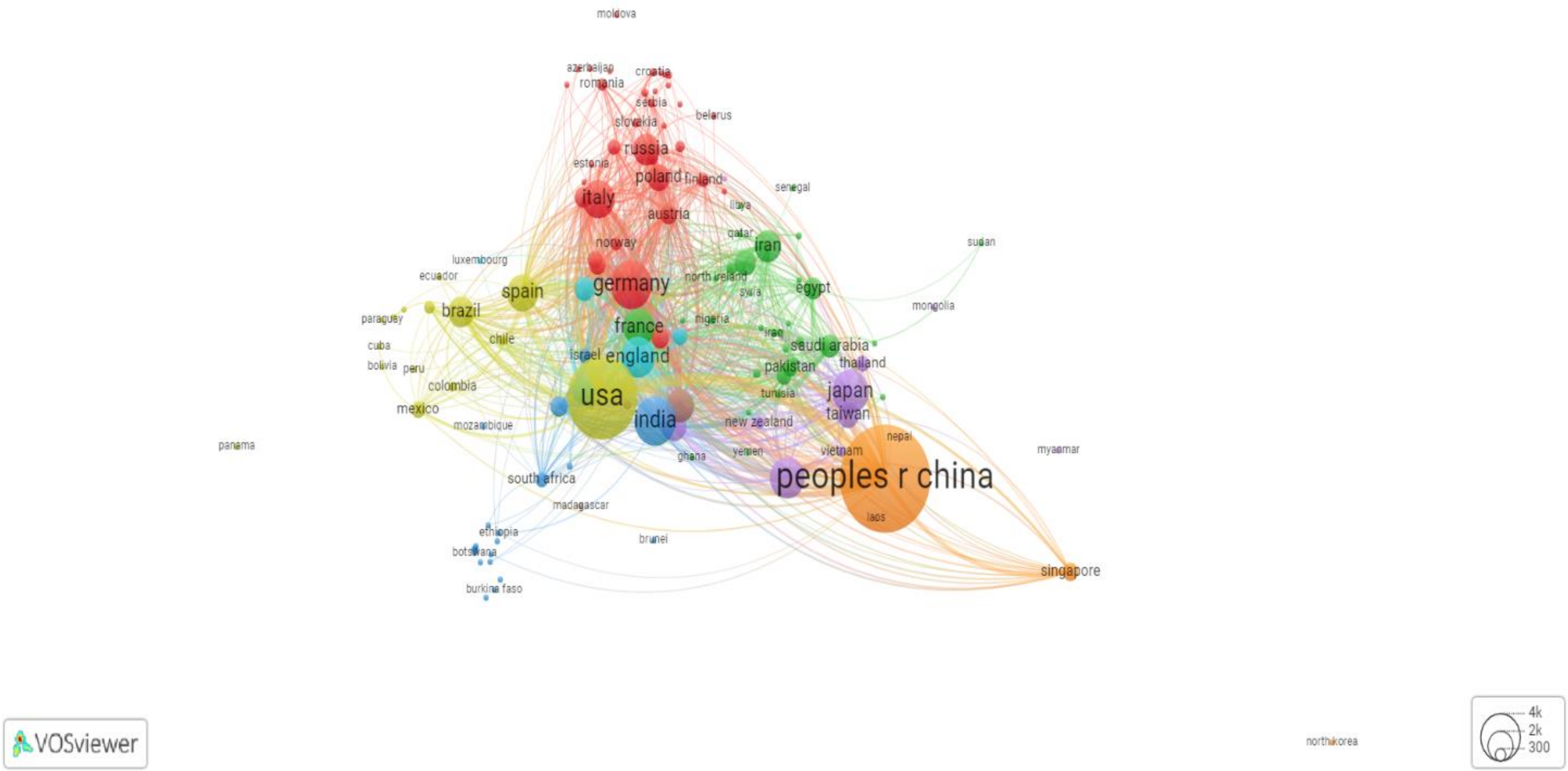
Source: Own elaboration using VOSviewer based on WoS data

Countries

The evaluation of countries based on the number of publications mirrors the institutional network previously analysed (Figure 15). While the People's Republic of China has the more sizable portion of publications, the small number of links with other scientific institutions outside of Asia pushes China to the outskirts of the map (Figure 15). On the other hand, many countries with decent levels of scientific production in the biosensors field, such as the USA, Germany, France, England, and India, have substantial synergies, which places those countries in the centre of the network.

While some countries have a substantial number of publications, they may occupy less prominent positions in the network. For example, Brazil and Spain, with strong connections to the South American market but a weak link with more central countries (exception made to the US). The same happens with Poland and Italy, which strongly associate with Germany and are well integrated into the European market, although they do not establish links with other geographical locations. The same can be said for Iran in Middle Eastern and North African markets (Figure 15).

Figure 15. Network distribution by countries



Source: Own elaboration using VOSviewer based on WoS data

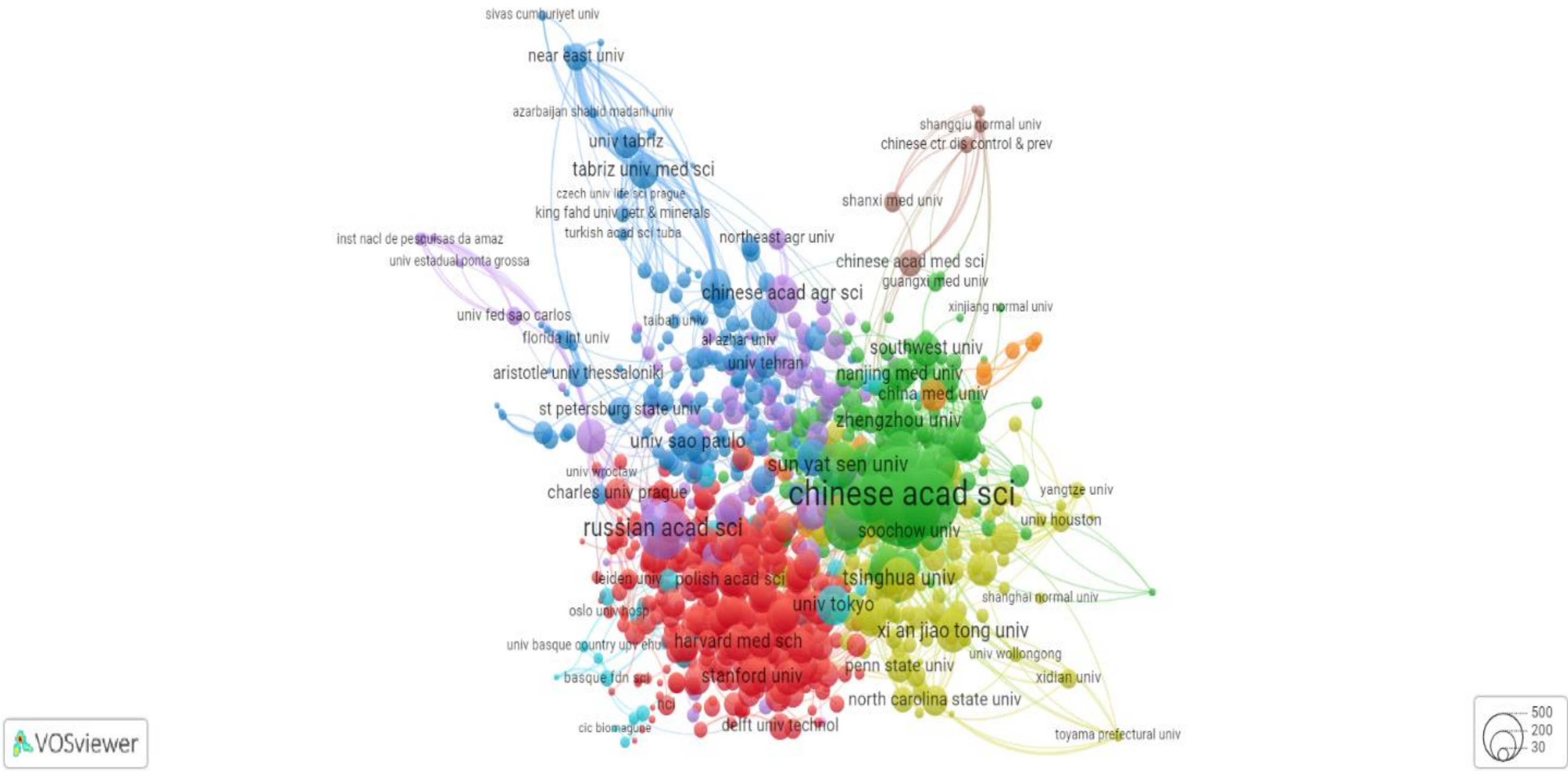
Cited organisations

The network distribution of the organisations by the number of citations is more homogeneous than the one based on the number of published articles (Figure 16). The Chinese Academy of Sciences is still the most notorious institution of this network (Figure 16), with a slight difference from the previous networks. It is closer to the middle of the map due to having tighter relations with other Chinese and Southeast Asian institutions.

It is visible an upbringing of institutions that were not noticeable on the previous maps. Stanford University (USA), the Polish Academy of Sciences (Poland), the Sun Yat-Sen University (China) or the Aristotle University of Thessaloniki (Greece) gained a new dimension with its work being heavily recognised and cited by academics worldwide. Other prolific institutions that transitioned from the previous map to the cited organisations map by keeping their strong relevant positions include the Russian Academy of Sciences (Russia), Tabriz University (Iran), Tokyo University (Japan) and the University of Sao Paulo (Brazil).

The clusters generated were still evident and similar to the map above (Figure 15); however, the aggregation of institutions near the centre appears denser and more interconnected. This indicates that these institutions have received substantial citations and recognition for their contributions in the biosensors field.

Figure 16. Network distribution by cited organisations



Source: Own elaboration using VOSviewer based on WoS data

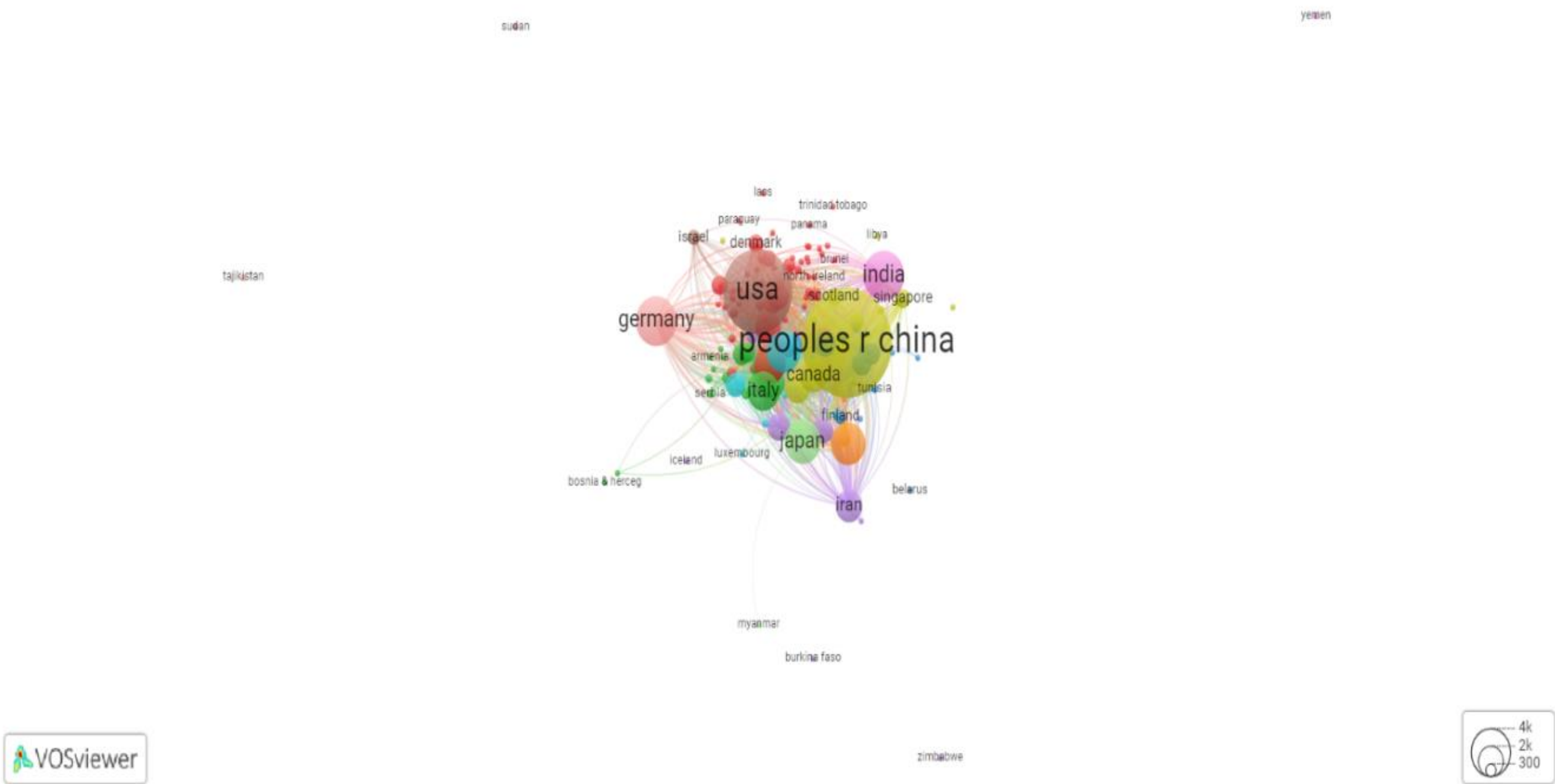
Cited countries

The cited countries have a distribution similar to the cited organisations' network (Figure 17). All the countries gravitate around the centre of the map, establishing strong links between them. The People's Republic of China is the most cited country in the biosensors field. However, it dialogues and has interconnections with all the other medium-sized countries regarding the production of scientific literature in the field (Figure 17).

The USA is highlighted in this map as the second most prolific country in the number of citations. It occupies a privileged position compared to other countries with a significant body of literature about biosensors less cited than the USA. Those countries include India, Iran and Japan in Asia, Germany and Italy in Europe, as well as Canada in North America. Nonetheless, India and Canada showed evident relevance growth in the cited countries' dimension; although they are not among the countries with the most publications in the field, their research works are often cited by other scholars.

Iran's position on this map is again symptomatic of a steady number of publications and citations (Figure 17). While being an island of knowledge within the global market, with most mentions occurring among national authors, it has few connections to other scientific locations. Germany's position in the network is interesting. Despite having many citations (leader in the European scenario) and a few connections with smaller scientific biosensors' markets in the EU, it is far from having a strong linkage with the leading countries such as the USA and the People's Republic of China.

Figure 17. Network distribution by cited countries



Source: Own elaboration using VOSviewer based on WoS data

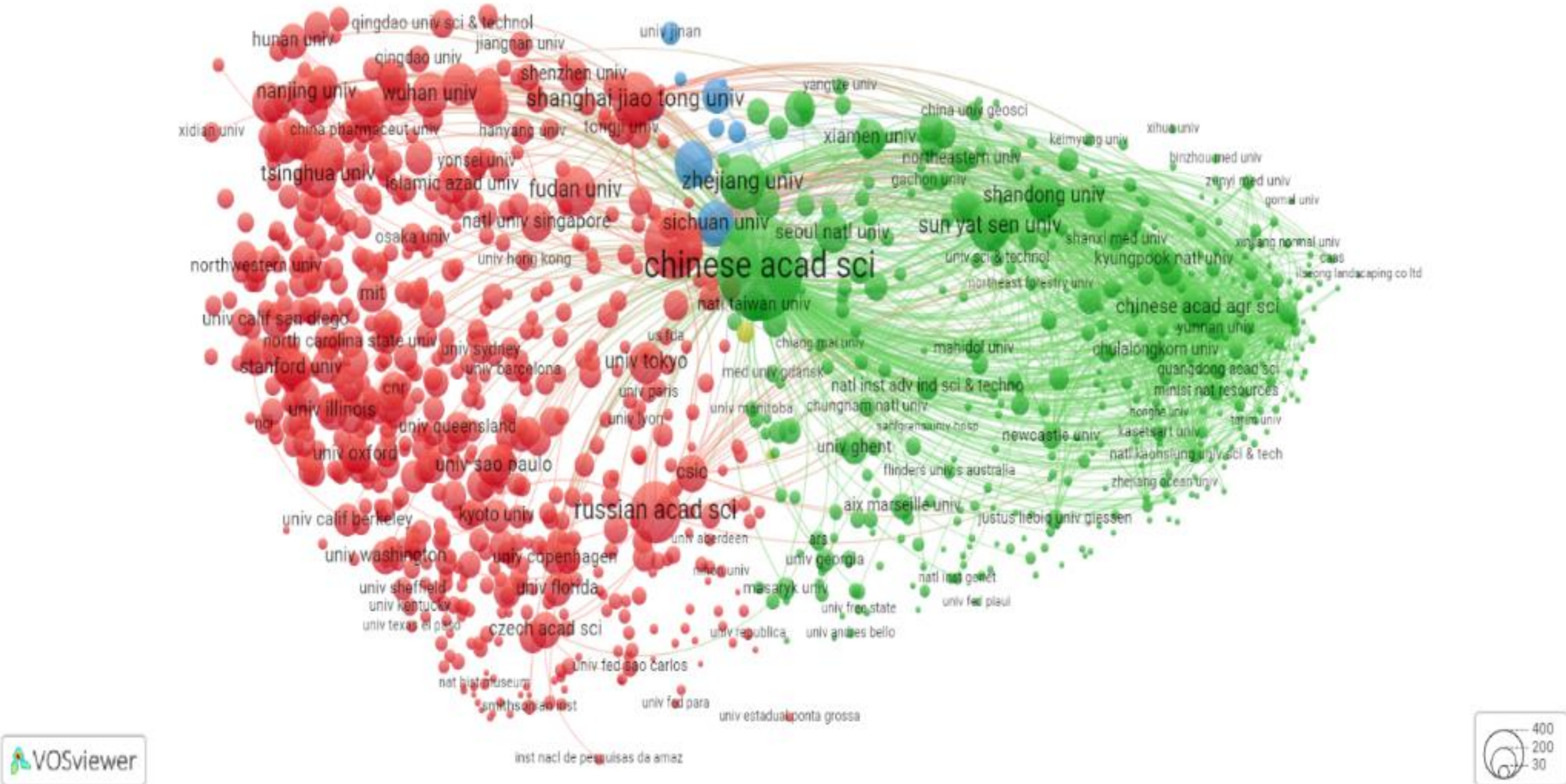
Coupling organisations

The coupling organisations network maps the institutions referenced in scientific papers to the same third organisation/institution (Figure 18). The network is divided into two big groups of institutions. In green are the Universities directly connected to the Chinese Academy of Sciences, which is hegemonic in the biosensors' field and have direct connections with a broad network of Asian and Chinese universities. This group is illustrative of the epistemological homogeneity of Chinese universities; however, it also includes Ghent University (Belgium) and Flinders University (Australia).

In red (Figure 18) is a vast agglomerate of international institutions that have mutual references in their scientific works with diverse geographical locations, but with prominent representatives in the Russian Academy of Sciences and the University of Tokyo.

Interestingly, when looking at the accumulations of red dots most distant from the centre (Figure 18), the presence of anglophone universities that are top references in the international rankings is visible. The University of Oxford, the University of California Berkeley and Stanford University are all part of this epistemological community, which are far from the Chinese Academy of Sciences but are in quite a close position relative to each other.

Figure 18. Network distribution by coupling organisations



Source: Own elaboration using VOSviewer based on WoS data

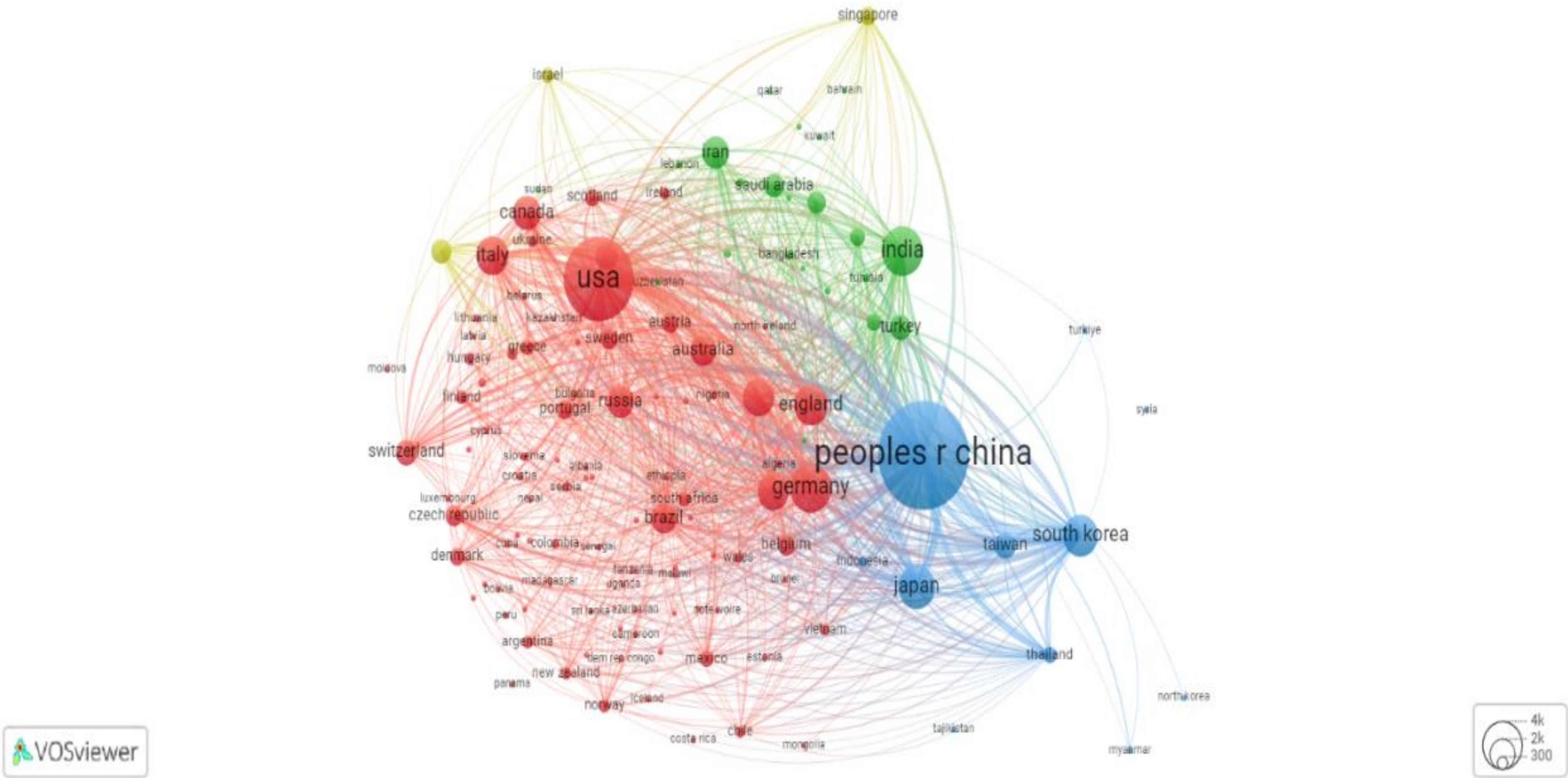
Coupling countries

The network of countries by coupling citations emphasises the presence of diverse small countries inside the biosensors' field (Figure 19). This is an essential trait in democratising innovation policy literature, as this dispersion is a synonym of research quality worldwide, including the global south. The same predominant countries keep their leadership in the field (Figure 19), with the USA being a close second to China and without any countries in sight with the potential to trouble this balance. There has been a growth in the citations mentioning India, England, Canada and Italy, although they have been gaining relevance inside their niches of coupling citations.

The anglophone world is aligned with most of the European countries and Russia in the network's core (Figure 19), due to the strong bonds established between them. However, the synergies with the green group of India and the Middle East or with the blue group dominated by China with the significant presence of Japan and Korea are not visible on the map.

The challenge for scientific production in the biosensors' realm is understanding how dialogues can emerge from this different nucleus that seems to be epistemological. This dialogue will help build strategies to synchronise the goals of the dominant markets such as China, the USA, the European Union, Russia and India to democratise the biosensors distribution. This requires a constant financial effort by countries with labs and research centres that can promote this intercultural and interdisciplinary dialogue to allow universal access to health care or environmental risk mitigation through biosensors that could be put to good use by the global population.

Figure 19. Network distribution by coupling countries



Source: Own elaboration using VOSviewer based on WoS data

BIOASSEMBLER

Integrating bio-inspired assembly into semiconductor manufacturing technology for biosensors

6. The Biosensors' future

6.1 Forecasting the biosensors potential

The future of the biosensors field is as important as its present; for that reason, it is crucial to understand the envisioned next steps in this market, considering the latest trends. To support the mass commercialisation of the product, strategic decisions must be taken to prevent financial and environmental losses so that the nanotechnology field can grow, supported by a solid foundation of sustainable chemistry.

Multiplexed sensors can simultaneously detect multiple biomarkers, improving accuracy and enabling early diagnosis of disease. Thus, multi-detection approaches have been emphasised in developing next-generation sensors (Beduk et al., 2022). Beduk et al. (2022) consider using multiplexed bio-(chemical) sensors, as an evident and attractive approach, especially for small sample volumes.

New application areas emerge as the literature focuses more on biosensors as an autonomous area of activity that can adapt itself to the needs of customers and in-need populations. The network maps presented in section 5 pointed to a trend for scientific organisations from different geographical locations to work together towards the progress of research and innovation.

The fostering of innovative technology production methods related to the sustainable transition and the green chemistry principles puts European countries such as Germany, the UK and Italy at the forefront of the biosensors field. The growth of green chemistry in Europe will represent an increase in the number of patents produced in the market of sustainable microelectromechanical sensors. This expansion, followed by the rise of the BRICS, challenges the Chinese Academy of Sciences' dominance in Asia and the global hegemonic position of the US in the semiconductors industry. The tendency to get different epistemic communities together through partnerships, being the USA-China's most sounding example, also contributes to global knowledge transfer and mitigates market disparities. Moreover, the gradual movement of universities and research centres from peripheral areas of the network maps towards the centre, through partnerships with highly reputable institutions, contributes to a more equalitarian environment in innovation academic markets.

The state-of-the-art points towards a positive trajectory of scientific production of biosensors with a steady international pace moving through different partnership and competition dynamics. As the literature shows, a broader application of this nanotechnology can more directly impact the chemical industry. The chemical industry is unique in its relationship with biosensors. While in the other markets analysed in this report the biosensing devices are end products aiming at being sold to use their different applications, in the case of the chemical market it is fundamental for elaborating the biosensors in all production phases. The keywords selected to build the networks displayed above are intrinsically related to the biosensors' production chains. The relevance earned by words such as design and performance in the results of this research illustrate the need of the producers to adapt to the client's needs, which implies requiring smaller, more accurate and comfortable devices.

The production of devices with those characteristics might undermine the stability and reliability of the biosensors, which prevents the technology from leaving the wearable self-tracking devices for more effective medical use. The optimism gravitates around the literature of biosensors as a critical healthcare device, although the field is still lacking further depth. Chemical synthesis plays a vital role in the pharmaceutical industry, enabling the research and development of new medicines. The biosensors are also essential for diagnosing viruses, as the genomes of different viruses can recombine to form new progeny, making it difficult to detect using only one biomarker.

The massification of biotechnology devices for general use of the population requires changes in international law frameworks. For civil society to feel safe using biosensors, there is a need for an international data protection policy while using self-tracking devices and for a more transparent and broader dialogue on scientific developments in the field of biosensors.

Also related to public health, biosensors have gained prominence in the food safety market. Evaluating food pathogens is also a frequent topic in this biosensor industry. Various food-quality biosensors exist (Bunney et al., 2014). The typology of biosensors applied in pathogen detection is not only based on enzymes, but instead is heavily dependent on the sample size and type. For example, to analyse nucleic acids, the most conventional methods are microfluidic PCR biosensing devices (Bhalla et al., 2020).

The biosensors are thought to help the agricultural procedures for healthier feeding habits; however, for that to happen, some severe pondering about the assessment of the life cycle of these technologies is required. The possibility of biosensors contaminating the environment after their disposal turned nanotechnology into an issue when it was conceived as a solution for environmental hazards.

6.2 Possibilities of short-term commercialization

New fields for biosensor applications are emerging while these devices become more sustainable, efficient, and cost-effective. In line with the food quality assessment, biosensors can be applied to the entire food chain by tracing agricultural production's health risks and evaluating possible food fraud cases (Griesche & Baeumner, 2020).

Besides, other more vanguard solutions can be given to biosensor usage, such as toxicological investigations in natural environments. Studies focused on the importance of biosensing in the toxicological assessment of algae (Pescheck et al., 2022); other authors emphasized the role of biosensors in tracking of biofilms structures that can bring negative consequences on public health (Saccomano et al., 2011).

The role of biosensors in the sustainable agriculture and food industry market is becoming more prominent, given the continuous growth of the world's population that will create new challenges to the efficiency of natural resources. Therefore, being able to detect food contamination during the storage and processing stages ensures food quality and averts potential health crises.

Applying synthetic fertilizers and other chemical products can improve agricultural production, avoiding contamination and promoting a more sustainable agri-food industry. Expanding the use of biosensing devices to monitor pesticides, toxins and pollution in real-time is one of the most valuable features of MEMS in the market. Improving detection time is essential for the widespread adoption and mass production of biosensors. It must value a cost-effective multiplex solution while maintaining high sensitivity to be successful and competitive. Additionally, quality control tests of the biosensor production should work towards reducing the storage costs, while facilitating its introduction in the market.

6.3 Mitigating Industrial Risks

Managing or treating chemical wastes requires sophisticated technical and technological setups (Chaaban, 2001; Hussain et al., 2022). Moreover, the risks associated with the environmental dimension of nanotechnology production are also addressed to mitigate the long-term prejudice that those can cause regarding the disposal of microplastics in the open air. A pre-generation waste minimization approach, known as source-level waste minimization, can be preferred over post-generation treatment and management initiatives for chemical industry-produced waste (Chaaban, 2001) in light of markets and technologies in BioAssembler corresponding economic, technical, and hazard-related concerns. It is possible to consider source reduction and waste minimization as initiatives to minimize chemical waste at the source level (Chaaban, 2001; Hussain et al., 2022).

The chemical industry dramatically relies on fossil fuels, such as petroleum oil. As a result of the limited availability of this non-renewable resource, in addition to the increasing demand for energy in developing countries and the consequent rise in oil prices, it is necessary to consider renewable resources as viable alternatives (Muffler et al., 2011).

However, it is essential to note that scientists warn that synthetic substances contaminate Earth's systems and that even if chemical production slows down, humankind has already flooded the atmosphere, hydrosphere, cryosphere, geosphere, and biosphere with own creations (Cassella, 2022). Since many of these chemicals can persist in the environment for a long time, their potential threats may continue to cause problems currently being overlooked.

An international team of researchers identified nine boundaries that keep the planet stable for human existence, including greenhouse gas emissions, the ozone layer, forests, and freshwater. Four of these boundaries were breached by humanity in 2015, such as climate change, greenhouse gas emissions, land-system change, and extinction rate. As stated by scientists, nations need to limit the overproduction of synthetic chemicals and evaluate those they already own. As the circular economy needs to be shifted (i.e., material and product design should focus more on reusing than wasting), products should be designed for recycling, and chemicals should be screened for their safety and sustainability along their whole impact pathway in the Earth system (Cassella, 2022).

7. Conclusion

This report highlights recent changes in biosensors and photolithography and how these can drive the recommendations for different geographical markets and diverse applications. It also highlights why biosensors require an innovative and transdisciplinary view and how this versatility can lead to more complex outcomes that consider and balance multiple dimensions of science, society and markets.

Biosensors research and markets are facing some challenges to further develop the technology in the market. There is a widespread intention and need for biosensors to accelerate real-time detection and measurement; this includes increasing sensitivity, one of the most fundamental dimensions of biosensors. Sensitivity is closely related to the attempt to reduce readout times, which depend on the type of technology associated with the biosensor. Nevertheless, the aim is to promote R&D activities that can reduce the readout time across all biosensor devices.

The lifespan of molecules and enzymes needs to be increased in order to implement long-term stable biosensors, while avoiding pre-treatment processes that delay their response time. This progress would be a sign of positive technological development in the field. In addition, miniaturisation in nanotechnology presents challenges in maintaining the efficacy and composition of biosensors while reducing their size.

Despite the competitive dynamics between different geographical markets in R&D and innovation, the triple helix based on partnerships between research centres/universities, industry and governments is central to the development of innovative products, and needs to be promoted. The emergence of new universities in the international scene from countries that were previously on the periphery of the nanotechnology market, such as the BRICS and at a smaller scale the UK, Italy, Poland or Greece, opens a chapter of diversification in the origins of technology patents, which could lead to more interconnected collaborations between different partners. Encouraging new consortia with creative approaches to the production of biosensors is one of the driving forces of innovation, and public and private entities must stimulate this dynamic to lead to more reliable and stable nanotechnology.

It is essential to address the legal barriers under the EU Data Protection Directives, which can threaten the democratisation of the biosensor market and push the boundaries of this nanotechnology. Firstly, it is essential to ensure the accuracy of biosensor results in order to create the conditions for the emergence of a legal framework at European Union level that allows the use of data provided by this technology for professional medical use, which still needs to be implemented. As mentioned above, the ability to promote stability and reliability of the materials used in the production of biosensors will be detrimental to providing the EU institutions with the confidence to trust the output of biosensors in the case of health data.

Moreover, the privacy concerns raised by experts and users regarding the possible misuse of personal data are a priority to address public support towards the innovative trajectory of this technology. As such, this must be addressed by actors – from scientists and innovators to regulators and NGOs – in coproduction with the development of the technology.

In addition, biosensor manufacturers should strive to reduce the size of devices without incurring high production costs. Inflation in the biosensor market would hinder its exponential growth and mass adoption, especially in POC services in healthcare. In this context, the product of the BioAssembler project opens up new possibilities for biosensing applications, including the sustainable mass production of a molecular biosensor aimed at the simultaneous detection of multiple health-related problems and the monitoring of response to medical treatment.

However, there are economic, political and structural factors related to the clustered markets in which biosensors operate that make this technology an unknown potential innovation prospect. Understanding the scope of the technology is fundamental to understanding the possible areas of activity and the challenges posed by the introduction of a new multiplexed biosensor.

The significant investment at industrial and scientific level has driven biosensing technology forward. This is evidenced by the increasing number of publications and patents registered in international databases. The wide range of applications of biosensors, from chemistry to healthcare, environmental monitoring or forensics, makes it a prospect for a sustainable transition in a future expected to be marked by environmental and public health risks.

The novelty and versatility of multiplexed biosensors has made the field an unsettled ground where practical use, economic profit, environmental hazards and social risks are part of a fragile equilibrium where all the vertices must be aligned to produce a sustainable and user-friendly product. This product will deliver faster and more reliable results with reduced environmental impact. Future research paths can shed light on the relationship between industry and universities in building an intelligent, sustainable transition, coloured by the advent of technology.

This business side of the deal needs to be complemented by paying close attention in future studies to people's perceptions of the use of biosensors, especially if the aim is to make it feasible for the wider population. At the policy level, an environment of mutual international cooperation between far-flung fields of activity is needed to create the conditions for easy adaptability of the technology, human resources and knowledge needed to democratise the use of biosensors. Stakeholders should continue to promote efforts to establish a framework that can ensure a balance between the natural and social sciences in order to weigh up all the factors involved in the production of new biotechnologies.

The BioAssembler project brings together experts from different sides of the scientific spectrum (Exact Sciences, Natural Sciences and Social Sciences and Humanities) to work on a label-free silicon biosensor production method that redefines the sustainability of the technology lifecycle and STEM R&D. This project will further develop the potential for massification of biosensor production in Europe, closing the development gap with the hegemonic innovation positions of the US and China in the semiconductor market. In addition, BioAssembler is essential for building new knowledge and technology networks, involving possible new partners from academia, industry or government to create synergies for progress on multiplexed biosensor devices. Finally, the concern of the project to communicate the results in an accessible way to the population that will be the users of the technology can open new links between universities and the general population. In this way, society can benefit from and make use of the innovations developed in the academic environment, while at the same time promoting a more fruitful and trusting dialogue between all the partners involved.

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