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Opinion

Redefining biomaterial biocompatibility: challenges for artificial intelligence and text mining

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The surge in 'Big data' has significantly influenced biomaterials research and development, with vast data volumes emerging from clinical trials, scientific literature, electronic health records, and other sources. Biocompatibility is essential in developing safe medical devices and biomaterials to perform as intended without provoking adverse reactions. Therefore, establishing an artificial intelligence (AI)-driven biocompatibility definition has become decisive for automating data extraction and profiling safety effectiveness. This definition should both reflect the attributes related to biocompatibility and be compatible with computational data-mining methods. Here, we discuss the need for a comprehensive and contemporary definition of biocompatibility and the challenges in developing one. We also identify the key elements that comprise biocompatibility, and propose an integrated biocompatibility definition that enables data-mining approaches.

Highlights

Biomaterials designed to interact with living systems should be evaluated for their biocompatibility; however, current definitions of biocompatibility are ambiguous and not well delimited.

The need for a consensus on the definition of biocompatibility complicates the understanding of its practical requirements, rendering data extraction difficult.

A working definition of biocompatibility will enable the use of computational tools to extract relevant information and perform reasoning.

Analyzing the international standards allowed us to include relevant specifications in the working definition of biocompatibility and identify useful vocabularies for text mining.

Charting the key elements and gaps in existing biocompatibility definitions enabled us to narrow down a unified and implementable working definition matching automated data extraction requirement.

What does it mean for a biomaterial to be biocompatible?

Biomaterials are materials engineered to direct the course of a therapeutic or diagnostic procedure by interacting with a living system or its components [1]. The biomaterials field has gained much interest in the past two decades due to the functional role they play in medical applications. By virtue of their use in biological applications, **medical devices** (see Glossary), and **advanced therapies**, biomaterials benefit patients and society by improving healthcare outcomes, increasing longevity, and enhancing quality of life.

Historically, biomaterials have primarily been employed as structural supports to aid healing and restore functionality [2]. Whilst commonly used as **prostheses** in cardiovascular, orthopedic, dental, ophthalmological, and reconstructive surgery, biomaterials are extensively used in other medical applications, including drug delivery systems, imaging contrast agents, and tissue engineering constructs [3]. Before the 1950s, understanding the interactions between the body and materials used in medical applications was crucial due to the relatively low probability of implant success [4]. In the past two decades, the functional deficit of these devices has streamlined efforts to better understand the interactions between materials and living systems [5]. These interactions and their related features are usually nested within the term 'biocompatibility' [1–6] and daughter processes including **biofunctionality**, **bioinertia, bioactivity**, and **biostability**. Given the importance of having minimal **adverse effects**, such as local or **systemic**, **subacute** or **subchronic toxicity** in the receptor tissue or organism, it is essential to carefully design biomaterials for a specific therapeutic or diagnostic function, ideally maintaining any effects within the boundaries of typical physiological ranges [7]. In clinical practice, biomaterials are rarely used independently but more often as part of a medical device. Evaluating the biocompatibility of medical

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devices is a multistage process encompassing all product development stages from the initial material screening to nonclinical and clinical safety evaluations, and from product release testing to post-market monitoring and periodic **product audits** (Figure 1).

To understand the assessment of biomaterials in the context of biocompatibility, it is crucial to be aware of the regulatory framework and life cycle of biomaterials. Regulations such as EU 2017/745 on Medical Devices[i] or those by the Center for Devices and Radiological Health of the FDA require proof of biocompatibility for all materials that come into contact with patients or users in the form of, or as part of, medical devices[ii]. Medical device evaluation to manage biological risk – as described in some of the standards of the **International Organization for Standardization (ISO)** 10993 family (Figure 2) – focuses on compiling toxicological data on material chemical components and leachable and degradation products, as well as both *in vitro* (e.g., cytocompatibility, **genotoxicity**) and *in vivo* (e.g., safety and efficacy in animal models) testing data (Box 1). Clinical evaluation of medical devices 'first in human' and pivotal clinical trials, as well as **post-market surveillance**, add biological risk data to the preclinical dataset. Problems due to biocompatibility are 'associated with undesirable local or systemic effects due to exposure to medical device materials or leachates from those materials, by a patient who has an implant or is receiving treatment with a device made from them'[iii].

However, neither the European Medicines Agency (EMA) nor the FDA[iv] has compiled a robust definition of biocompatibility, but rather they refer to the tests required for regulatory approval.

The growing interest in biomaterials research and innovation has led to a continuous increase in the volume of scientific literature and of data on or related to biocompatibility. This rapidly expanding research has centered on achieving maximal integration and acceptance of biomaterials by living systems, and further expanding the battery of parameters, tests, and data used to characterize these [8] (see Table I in Box 1). Assigning attributes to biocompatibility has been vigorously discussed over the past 50 years, and several definitions have been suggested (Figure 3). Among these, the most widely accepted were proposed by Professor David F. Williams, a key opinion leader in the field. These definitions focus on implantable devices for use in humans and, while useful in identifying important aspects of biocompatibility, they present critical gaps in failing to address adversity in a methodical manner. Particularly for text-mining applications,

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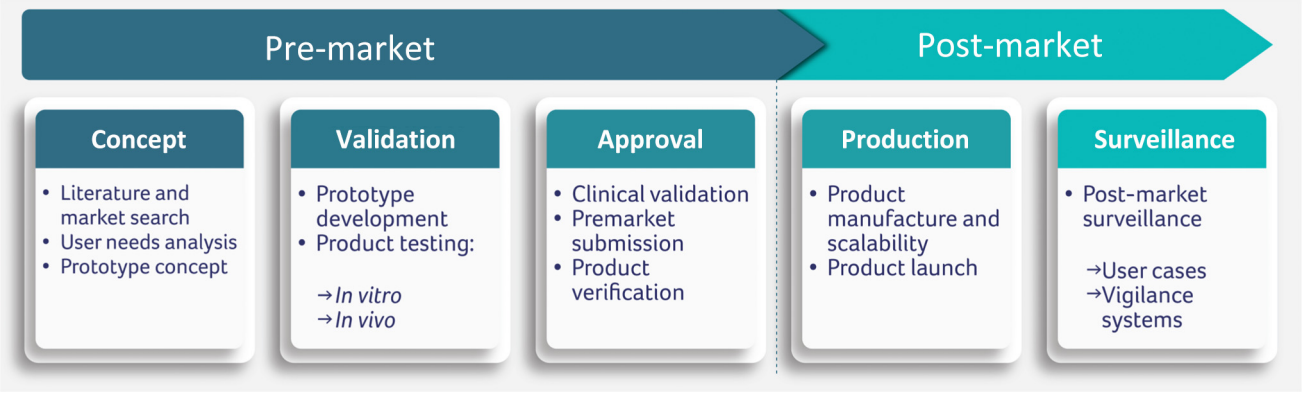

Figure 1. Medical device development and safety evaluation life cycle. The life cycle of medical device development and safety evaluation consists of distinct phases. Pre-market activities involve concept validation and regulatory approvals, ensuring that devices meet safety and efficacy standards. Post-market activities are mostly engaged with production and continuous surveillance to monitor device performance and safety in real-world settings, ensuring ongoing patient wellbeing.

these are either too general or too specific to enable a reliable application of these technologies. It is, therefore, apparent that the existing definitions of biocompatibility are limited or outdated [4], and the current framework of mechanisms and processes describing biocompatibility is inadequate.

Considering these limitations, it becomes apparent that updating the definition of biocompatibility will lead to a more comprehensive and contemporary understanding, enabling a more applicable framework for scientists, engineers, and healthcare professionals to work within. An updated definition of biocompatibility may initiate novel approaches to assess biocompatibility and promote more consistent and clear communication between stakeholders. Consequently, this could streamline the approval process for novel biological applications of biomaterials and medical devices, thus expediting their development and market entry (Box 2).

To address this, we aim to reconstruct the definition of biocompatibility to enable automatic data extraction from text into structured datasets. By successfully integrating a working definition of biocompatibility, automatic data extraction could replace the manual process of gathering and synthesizing biocompatibility data across studies and study types (Figure 4). This would not only considerably reduce the time for knowledge extraction but also allow for a standardized process that minimizes bias.

Why do we need a new definition of biocompatibility, and what are the challenges in developing one?

As stated previously, biomaterial design and evaluation have led to the generation of vast, diverse, complex, and heterogeneous biocompatibility data. These variations in biocompatibility data quality make them particularly difficult to assess. This can be attributed to the variability of parameters and experimental designs, the association with both qualitative and quantitative data, and a large volume of experimental outputs and consecutive data formats. Due to this versatility, gathering and synthesizing biocompatibility data across studies has been manually processed so far, especially at the preclinical stage.

Databases efficiently organize extensive data in a structured form to make it easily accessible, and are key in facilitating manual meta-analyses and dataset grouping to enable comprehensive data comparison. Also, databases enable data sharing, foster synergies and collaborations, and promote consistency, ensuring long-term data preservation. In the field of biomaterials, however, there are to date no available databases or structured datasets of biocompatibility data. The current dataspace comprises complex data incoming in myriads in real time. Thus, there is a need for automated tools like **machine learning (ML)** and AI to extract useful context across studies. Such tools can compile datasets, recognize hidden patterns swiftly and efficiently, and decipher data, therefore accelerating innovation and advancing knowledge across disciplines. These attributes make both databases and data extraction automation indispensable in biomaterials research and development.

In other scientific research areas there are well-structured vocabularies – **ontologies** and datasets (e.g., genomics and chemistry), computational tools like ML [e.g., **natural language processing (NLP)** and **text mining** tools] – that can be used to extract information from text into structured datasets, as well as to derive new insights from these [9–12]. For example, the relationship between different types of biological entities like genes, proteins, or chemicals is well defined and captured in multiple linguistic assets. As a result, the automatic extraction of relationships from text has become feasible [13,14]. After extraction, data can be integrated and used to perform more advanced tasks, such as prediction and discovery.

Glossary

Advanced therapy: medical products for human use that are based on genes, cells, and/or tissue engineering.
Adverse effects: undesired effects of a drug, device, or other type of treatment (such as surgery) that may range from mild through severe to life-threatening. Also called adverse events and adverse reactions.
Bioactivity: the responses after exposure to a substance, which may include tissue uptake, metabolism, or physiological response.
Biofunctionality: the functionality of a biomaterial.
Bioinertia: the tendency of a component to not alter any biological function.
Biostability: the ability of a material to maintain its physicochemical integrity after implantation into living tissue.
Carcinogenicity: the ability of a chemical substance or mixture of substances to induce cancer or increase its incidence on interaction with living systems.
Cytotoxicity: the degree to which a substance can cause cell damage, leading to cell death.
FAIR: findability, accessibility, interoperability, and reuse of digital assets.
Genotoxicity: the property of substances to damage genetic information within a cell, potentially driving mutations.
Hemocompatibility: substance properties that do not induce a significant degree of damage to blood constituents.
Host response: the reaction of living tissue to the presence of a foreign material.
Irritation: inflammation or other host discomfort caused by reaction to irritants.
International Organization for Standardization (ISO): an international nongovernmental organization, comprising national standards bodies, which develops and publishes a wide range of proprietary, industrial, and commercial standards.
Machine learning (ML): the use and development of computer systems able to learn and adapt without following explicit instructions, using algorithms and statistical models to analyze and draw inferences from data patterns.
Medical devices: any instrument, apparatus, implement, machine,

Additional examples showcasing the power of ML in related scientific domains include (i) materials science, where prediction of material properties, such as analysis of mechanical strength and electrical conductivity, can speed up the development of new materials like batteries, semiconductors, and advanced composites [15], (ii) chemistry, where rational design of novel molecules can deconvolute, for example, molecule–drug interactions, expediting the design of potential drug candidates [16], and (iii) molecular biology and pharmacology, where it enables discovery of undetermined associations between targets and drugs and may identify drug repurposing opportunities, thus accelerating drug development and reducing costs [17].

Using controlled vocabularies and well-defined data annotation criteria combined with advanced NLP techniques based on large language models [14] and transformer technologies can provide valuable resources that enable a more systematic access to and extraction of biomaterials biocompatibility information. These approaches require the use of manually labeled training data as examples to generate predictive models, which can then automatically infer how to classify, extract, or normalize biocompatibility-related data features.

Language models represent a critical technological advancement as they can capture or model human language in a way that both linguistic features and semantic aspects of written text can be exploited more efficiently for a variety of tasks such as text classification, automatic summarization, machine translation, **named entity recognition (NER)** [18,19], and concept mapping (e.g., biomaterial composition to concepts in ontologies or terminologies) [20]. Language models have already been adapted or fine-tuned for biomedical NLP tasks and could thus serve as resources for biomaterials text-mining scenarios. NLP uses ML to reveal text structure and meaning but requires fundamental steps such as parametrization, term categorization, standardization of vocabularies, and development of terminologies. To identify these key parameters, NLP tools require a consensus on biocompatibility as a first step. As such, an updated definition of biocompatibility plays a key role in enabling the use of these technologies in the biomaterials field.

Exploiting these tools for biomaterials text mining has been limited, further illustrating the need for a consensus on key definitions and uniform terminology. This can be attributed to both the complexity of the data (e.g., molecular, structural), the existence and use of a range of databases and resources, some of which might be sensitive (e.g., patient data), the variations in the way that data is made available (e.g., articles, patents etc.), and the interdisciplinarity of the biomaterials field. Further challenges are associated with insufficient awareness of the text mining potential for researchers and a limited familiarity with the different technologies available. Moreover, the lack of consistent and standardized terminology leads to further integration (e.g., biological vs. clinical) and validation challenges, ultimately making tool development highly resource-intensive. Nevertheless, the range of resources currently available can be used to harness key elements and attributes of biocompatibility or biomaterials-relevant entities from text [21,22] (Box 3).

However, additional refinement, evaluation, and adaptation focusing on the characteristics and needs of biomaterials data annotation are still required. For instance, automatic concept extraction and NER tools can generate text-derived terminologies or lexical resources to enrich and complement vocabularies and assist in developing terminologies that characterize biocompatibility information. A critical step for the use of text mining results is entity linking or normalization. This step automatically maps various expressions, terms, or abbreviations to their corresponding common semantic representation or concept identifier in a given terminology or vocabulary

appliance, implant, reagent for *in vitro* use, software, material, or other similar agent, intended to be used for a medical purpose.
Named entity recognition (NER): a type of data extraction that seeks to locate and classify named entities mentioned in unstructured text into predefined categories.
Natural language processing (NLP): machine learning technology comprising computational techniques for the analysis and synthesis of natural language and speech.
Ontologies: a set of concepts and categories in a subject area or domain that show their properties and their relations.
Post-market surveillance: a systematic process to derive corrective and preventive actions from information on medical devices already placed on the market.
Product audits: an examination of a particular product or service to evaluate whether it conforms to requirements (i.e., specifications, performance standards, and customer requirements).
Prostheses: devices designed to replace missing body parts or improve their function.
Sensitization: a process by which the immune system will produce an antibody in response to a substance.
Subacute toxicity: adverse effects occurring after administration of a single or multiple doses of a test sample per day given during a period of 14–28 days.
Subchronic toxicity: the ability of a substance to cause effects for more than 1 year but less than the lifetime of the exposed.
Systemic toxicity: toxic effects caused as a result of absorption and distribution of a substance that affects the whole body rather than a specific area.
Text mining: the process of transforming unstructured text into a structured format to identify meaningful patterns and new insights.

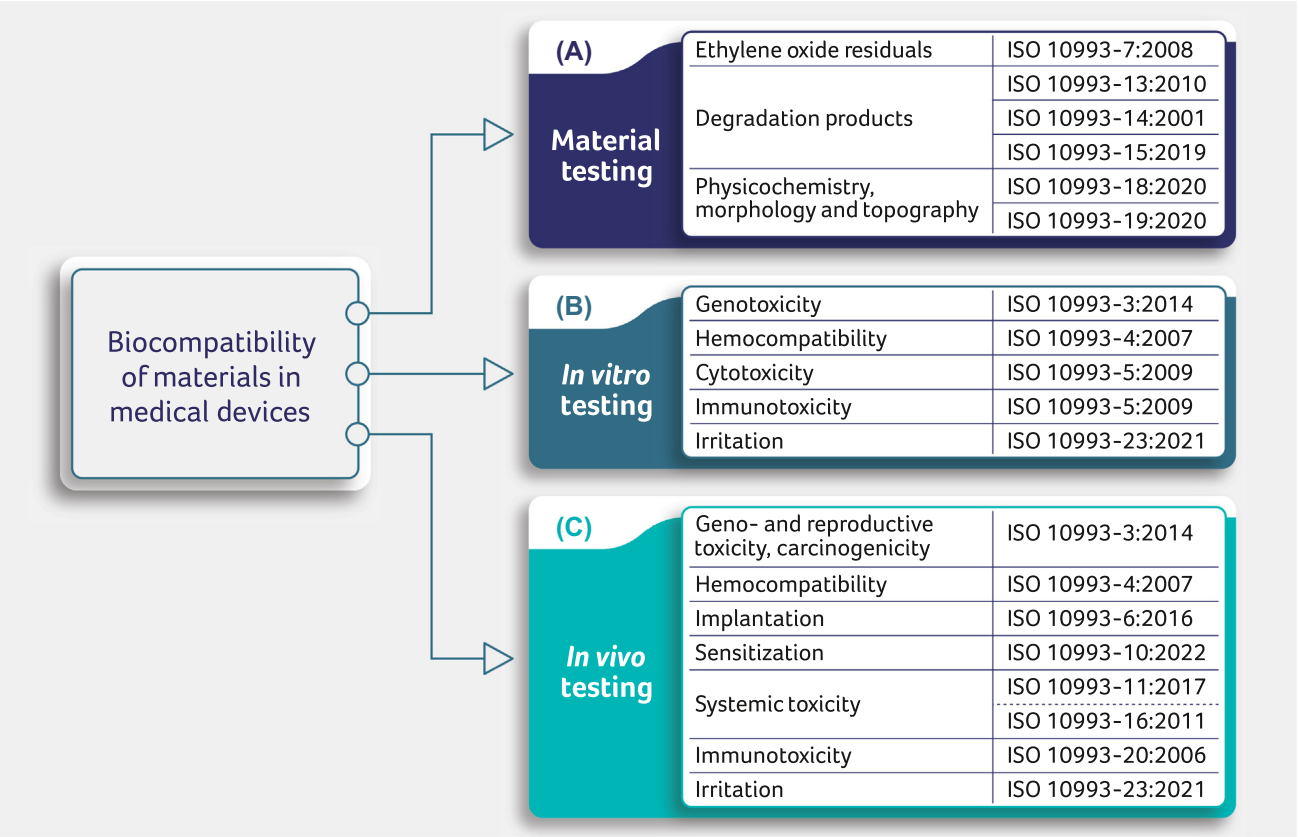

Figure 2. International Organization for Standardization (ISO) 10993 in brief. A schematic for identifying key elements regarding the biocompatibility assessment of biomaterials and their alignment with ISO 10993 specifications. This figure depicts the intricate process of conducting materials testing and also both *in vitro* and *in vivo* tests, essential for ensuring compliance with the stringent testing requirements of ISO 10993.

(see Table I in Box 3). Biomedical language models are also being explored to improve entity-linking strategies and to achieve automatic term mapping [23].

Biocompatibility is commonly regarded as a linear sequence of events directed by well-characterized processes in materials science and biology. In practice, however, this is not the

Box 1. ISO 10993: biological evaluation of medical devices

The suitability of biomaterials used for medical devices has to be investigated in compliance with the ISO 10993 standards. The primary aim of ISO 10993 is the protection of humans from potential biological risks arising from the use of medical devices, which are composed of biomaterials. This approach includes applying several tests enabling a full evaluation of the biological responses to each medical device, relevant to its safety in use, based on *in vitro* and *ex vivo* test methods and animal models. Biological responses that are regarded as adverse, caused by a material in one application, might not be regarded as such in a different situation. Thus, for a complete biological safety evaluation, ISO 10993 classifies medical devices according to the nature and duration of their anticipated contact with human tissues (Table I).

The role of ISO 10993 is to serve as a framework to plan a biological evaluation and not to provide a rigid set of test methods, including pass/fail evaluation. Where a particular application warrants it, experts in the product or in the area of application concerned can choose to establish specific tests and criteria, described in a product-specific vertical standard. In addition, material characterization is a crucial first step in the biological evaluation process. The extent of chemical characterization required depends on available preclinical and clinical safety and toxicological data, but, as a minimum, the characterization should address the constituent chemicals of the device and possible residual process aids or additives used in its manufacture.

Table I. The biological effects required to be evaluated according to ISO 10993[a]

Medical device categorization					Biological effect					
Category	Contact	Duration	Cytotoxicity	Sensitization	Irritation/ intra-cutaneous reactivity	Systemic toxicity	Subchronic toxicity	Genotoxicity	Implantation	Hemo-compatibility
Surface device	Skin	≤24 h	X	X	X	–	–	–	–	–
		25 h–30 d	X	X	X	–	–	–	–	–
		>30 d	X	X	X	–	–	–	–	–
	Mucosal membrane	≤24 h	X	X	X	–	–	–	–	–
		25 h–30 d	X	X	X	–	–	–	–	–
		>30 d	X	X	X	–	X	X	–	–
	Breached or compro-mised surface	≤24 h	X	X	X	–	–	–	–	X
		25 h–30 d	X	X	X	–	–	–	–	X
		>30 d	X	X	X	–	X	X	–	X
External commu-nicating device	Indirect blood path	≤24 h	X	X	X	X	–	–	–	–
		25 h–30 d	X	X	X	X	–	–	–	–
		>30 d	X	X	–	X	X	X	–	–
	Tissue/bone/ dentin	≤24 h	X	X	X	–	–	–	–	–
		25 h–30 d	X	X	X	X	X	X	X	–
		>30 d	X	X	X	X	X	X	X	–
	Circulating blood	≤24 h	X	X	X	X	–	–	–	X
		25 h–30 d	X	X	X	X	X	X	X	X
		>30 d	X	X	X	X	X	X	X	X
Implant device	Tissue/ bone	≤24 h	X	X	X	–	–	–	–	–
		25 h–30 d	X	X	X	X	X	X	X	–
		>30 d	X	X	X	X	X	X	X	–
	Blood	≤24 h	X	X	X	X	X	–	X	X
		25 h–30 d	X	X	X	X	X	X	X	X
		>30 d	X	X	X	X	X	X	X	X

[a]ISO 10993 mandates evaluation of the biological effects based on the nature and duration of contact between the medical device and the body, addressing local and systemic effects for short/long-term interactions to ensure device safety.

case. Biocompatibility is and should be interpreted under the prism of plasticity as a tiered multi-layered process, factoring inherent and transient genetic, epigenetic, and immunophenotypic parameters that may potentially influence the biocompatibility of a medical device [4]. Implementing a universally accepted definition demands that key challenges are defined and a flexible yet robust term is constructed. The biocompatibility of biomaterials includes a broad range of *in vivo* and *in vitro* assays (Box 4) which evaluate biological events such as cytocompatibility,

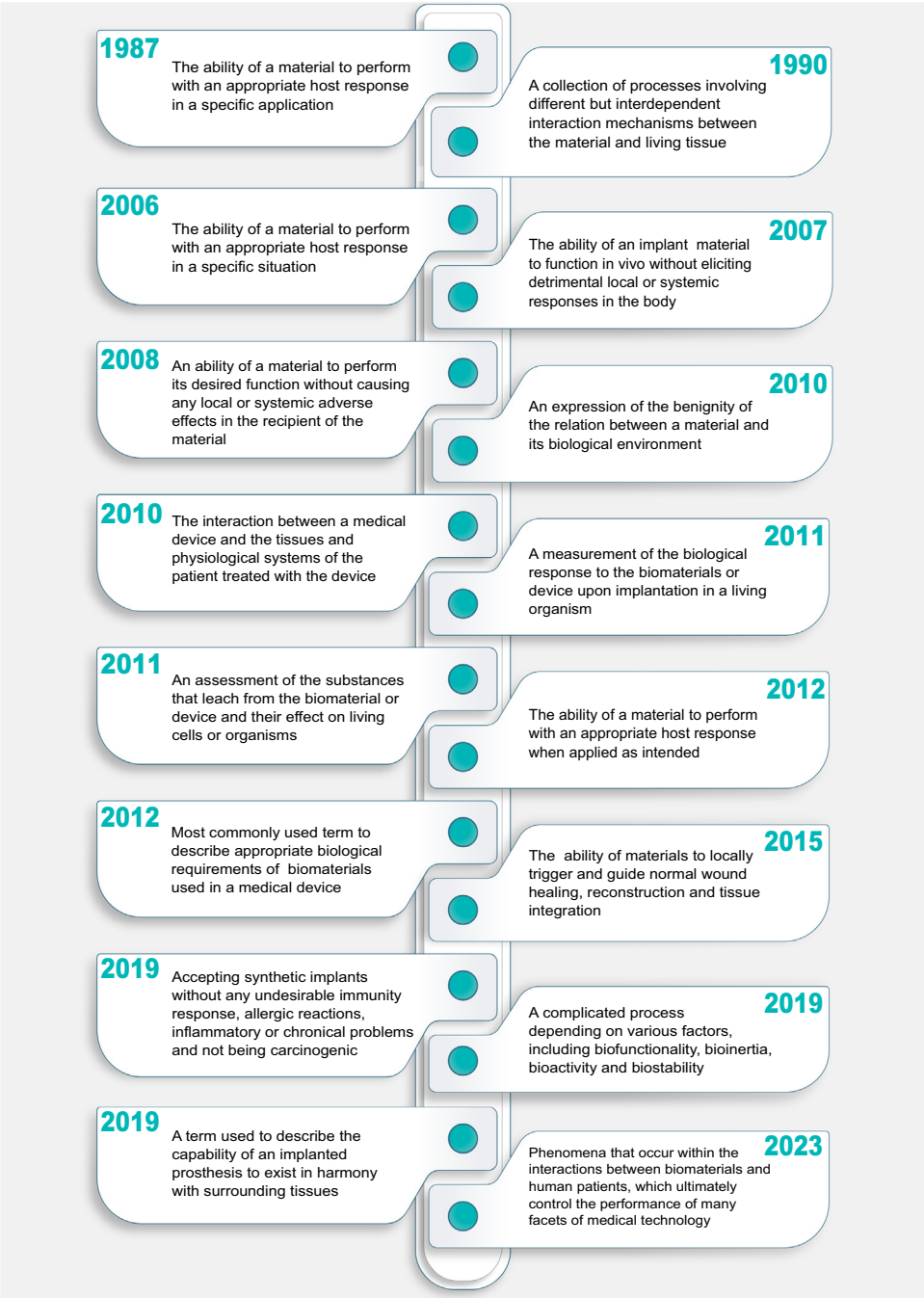

Figure 3. Biocompatibility definitions over time. A chronological representation of selected biocompatibility definitions extracted from the literature is presented, aiming to offer insights into the evolving understanding of the term biocompatibility and its attributes, over the past decades. These definitions were previously proposed in [4,7,35–43].

genotoxicity, duration of events such as acute and chronic toxicity, anatomical or tissue-specific effects such as **hemocompatibility,** reproductive and developmental toxicity, and severity such as **sensitization, irritation,** or **carcinogenicity**. Thus, the degree of biocompatibility is not

Box 2. Translating biocompatibility into added market value

The potential of AI to generate value in the biomaterials domain, particularly related to biocompatibility, remains vast and versatile. An area where both biocompatibility and AI-driven tools may prove key is drug delivery. Biomaterial delivery vehicles, such as lipid nanoparticles, can expand the range of tissues that drugs can reach, which is a major challenge for novel drug modalities such as gene and RNA-based therapies. In 2019–2021 alone, the unexplored delivery segment generated over US$2.3 billion in venture capital investment in privately held biotech companies[v]. Structured biocompatibility data would be invaluable for AI-enabled delivery vehicle design, potentially reducing expensive and cumbersome preclinical development.

Another area where biocompatibility data could prove transformational is in the clinical development of medical devices. Quality, or poor quality, in the medical device industry has been estimated to cost US$26–36 billion annually[vi]. These costs result largely from device failures and remediation. This is over and above adverse events, which also takes personal and societal tolls on patients[vii]. Data-driven design of novel biological applications and medical devices that considers accumulated historical data and biocompatibility learning from *in vivo* and clinical studies holds the potential to accelerate development, reduce costs, and improve patients' outcomes and quality of life.

easily defined. The development of advanced biomaterials should also be addressed at the level of partial tissue integration of biomaterials, further complicating materials' biocompatibility.

Proposing a new working definition of biocompatibility

Predictive and wet-lab methods are continuously being added to the toolbox of biocompatibility evaluation. Among these, methods have been developed for the characterization and quantitative evaluation of material degradation [24,25], load-bearing [26], and models simulating material corrosion assessment [27]. In parallel, predictive models have been developed: for instance, models of mechanical simulations for tissue properties characterization [28] and fluorescent approaches for *in situ* and quantitative testing of spatiotemporal materials, such as functionalized gels [29]. Other studies identify lags in the prediction of cell bioactivity, despite the robustness of the capacity of numerical models to predict the microstructure and bulk mechanical properties of materials [30]. Bridging biomaterials with the host's transcriptomic profile to define cellular and molecular biocompatibility further enhances the resolution of biomaterial applications [31,32]. Next-generation biomaterials incorporate stochastic biomaterial design [33] and embrace **FAIR** principles, enabling interactive web tools for *in silico* modeling of novel biomaterial and medical device microarchitectures. These tools offer cost-effective approaches for predicting and optimizing cellular responses, partially addressing biocompatibility concerns and potentially reducing expenses before full-scale experimentation and production.

The strategy builds on existing biocompatibility definitions used in the literature and international standards (Table 1) to extract their key components and group them in clusters. Table 1 provides a comprehensive summary of biocompatibility definitions extracted from published literature, by year and respective source, and offers insights into the strengths and limitations of these definitions, evaluating whether they effectively encompass *in vitro* or *in vivo* approaches. These key elements were then mapped (Figure 5) and used to integrate a working definition of biocompatibility.

This definition aims to capture the heterogeneous relationships between biomaterials and other elements, such as the material's structural and functional characteristics, the nature of contact with the host, and the outcome of exposure to the biomaterial, and the **host response**, in a specific manufactured object. Based on the most used definitions of biocompatibility, including both experimental and regulatory approaches, we aim to implement a more pragmatic, multilayered data-centric strategy that is useful for data extraction and annotation.

International standards, including ISO 10993, employ a range of tests to evaluate biocompatibility, aiming to classify medical devices according to the nature and duration of their anticipated

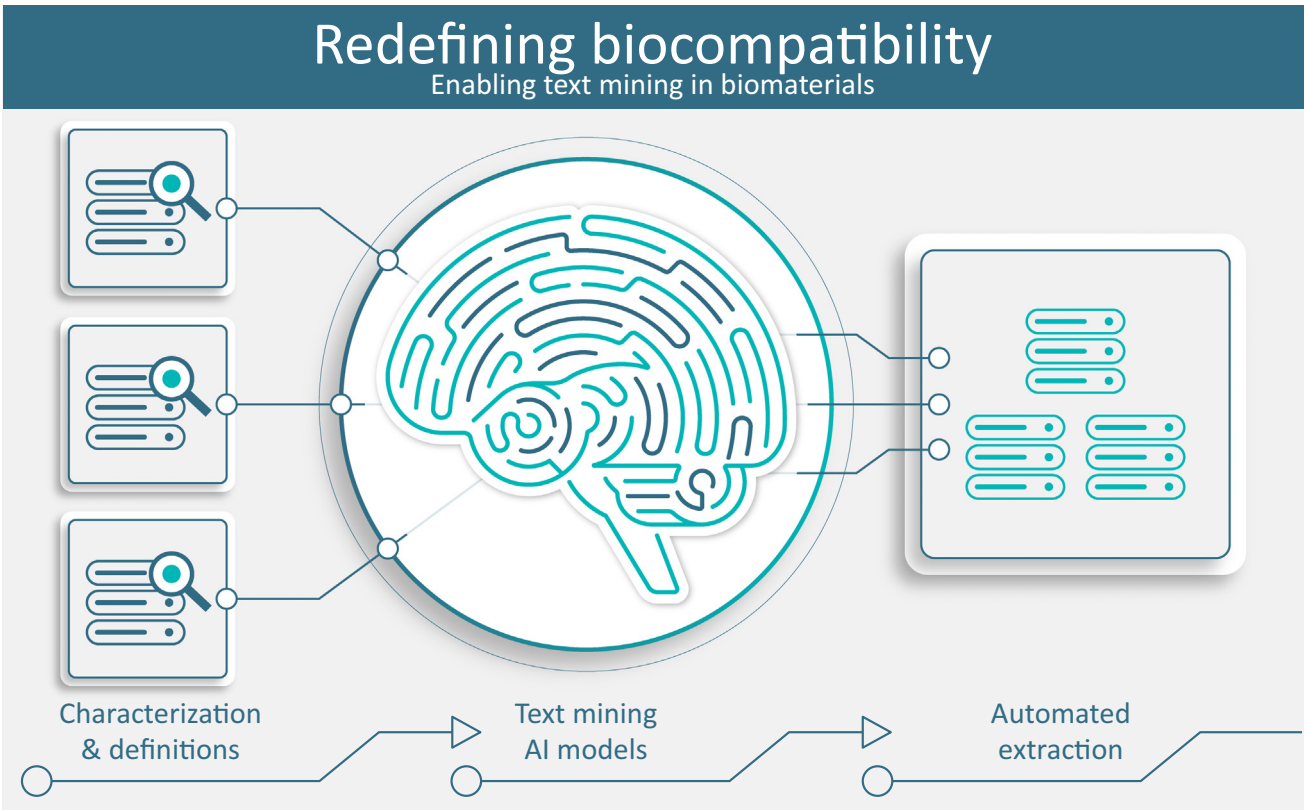

Figure 4. Harnessing text mining and artificial intelligence (AI) to redefine the concept of biocompatibility. This approach enables automated data extraction, facilitating a deeper understanding of biocompatibility through advanced natural language processing (NLP) techniques.

contact with the recipient. These tests comparatively measure the level and time duration of the adverse biological reaction (see Table I in Box 1 and Box 4). Biocompatibility was also often defined by the absence of adverse effects, essentially relying on the biomaterial or device not causing harm to be deemed biocompatible. Biocompatibility is, however, a composite term describing the dynamic interaction of the material with the host, and linked to: (i) material properties: the physicochemical, geometrical, and surface parameters of the material (e.g., size, porosity, surface texture, etc.) and the proportion of the material relative to the host tissue, (ii) interface: the nature of the contact between the material and biological components, (iii) location: the anatomical region of application, and (iv) duration: the length of the exposure (i.e., the duration of implantation).

Taking these factors into account, we propose an integrated definition of biocompatibility to serve as an input for the development and application of tools for information extraction into structured datasets and databases. We suggest that the term is extended to include these essential elements to aid the evaluation of the degree of biocompatibility. The proposed working definition is as follows.

Biocompatibility is the set of attributes describing the capability of a material to perform its desired function for the projected period of time without causing significant risk of local or systemic adverse response, irritation, toxicity, or any other adverse event in the recipient. The degree of biocompatibility depends on the material properties, the interface with the biological system, anatomical location, and the application duration or exposure time.

Box 3. Currently available tools

DEBBIE

The DEBBIE project developed fundamental text-mining resources and tools for the biomaterials domain. The tools included the DEB Ontology, the Biomaterials Annotator, and the DEBBIE database [41]. The DEB ontology formed the basis for computer-based knowledge representation, while the DEBBIE retrieval and annotation pipeline automatically curated and updated the open-access biomaterials database, containing over 350 000 annotated biomaterials abstracts. All these resources are freely accessible on the project's GitHub repositories and can be readily customized or adapted (Figure I).

Compendium for biomaterial transcriptomics (cBiT)

A repository of biomaterial-based transcriptomics data and biomaterial metadata populated with the host's transcriptomic profile to define cellular and molecular biocompatibility. cBiT[viii] aims to make materiomics studies and data publicly available which can be accessed directly by researchers or through requests to generate new data on a supplied biomaterial.

PubTator

An NER tool that enables automatic biomedical concept annotation in abstracts or open-access full-text articles [42]. PubTator annotates terms based on existing vocabularies, including the National Library of Medicine. Although not aimed specifically at biomaterials, it is a useful tool for mining biomaterials data.

BIOMATDB

The BIOMATDB[ix] project is an EU-funded initiative that aims to create an advanced database for biomaterials, providing detailed information on their properties and a web-optimized information marketplace and digital advisors.

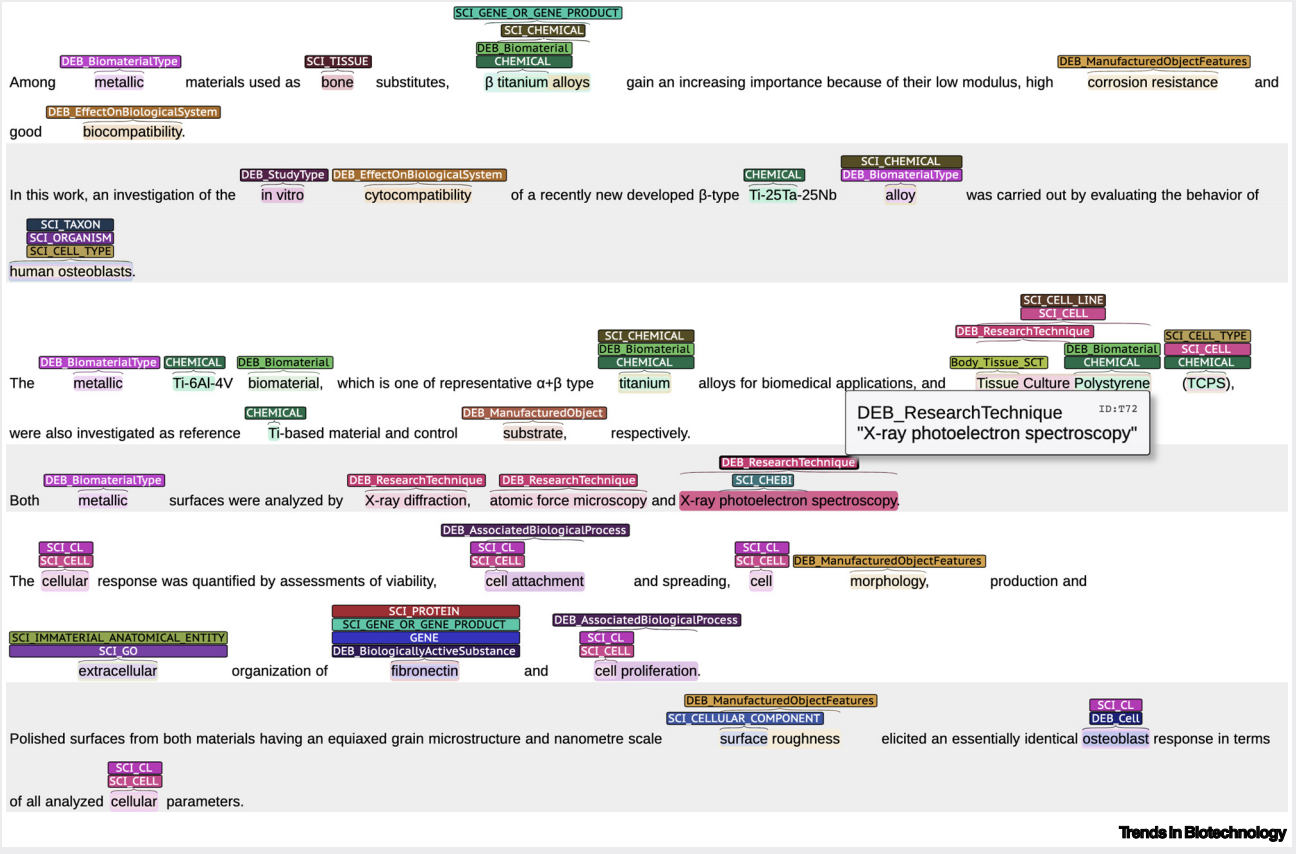

Figure I. Natural language processing (NLP) fine-tuning the quest for a new biocompatibility definition. This screenshot shows the results of various biomedical concept recognition systems, including results of the ScispaCy library and DEB Ontology term matching. It illustrates the usefulness and need for adapting and fine-tuning NLP technologies to the biomaterials domain, including biocompatibility characteristics.

Box 4. *In vitro* and *in vivo* techniques commonly used for the evaluation of biocompatibility

For the *in vitro* characterization, a wide range of assays can be employed.

- Fluid-based assays: quantify protein absorption using UV spectroscopy, colorimetric methods (e.g., bicinchoninic acid assay, Bradford, Lowry assay), ELISA, surface plasmon resonance (SPR), quartz crystal microbalance with dissipation monitoring (QCM-D), ellipsometry, and atomic force microscopy (AFM).
- Cell-based assays: assess **cytotoxicity**, cell viability, apoptosis, migration, oxidative stress, and genotoxicity. Methods include vital dyes, metabolic measurement, live/dead assays, mitochondrial potential, and DNA analysis.
- Blood and cardiovascular cells: thrombosis evaluation involves clot formation, platelet adhesion, prothrombin time, and thrombin production. Endothelization is assessed through endothelial cell migration, molecular characterization, and tube formation assays.
- Other cellular processes: qualitative and quantitative evaluation includes cell morphology, flow cytometry, fluorescent imaging, scanning electron microscopy (SEM), hemolysis index, leachables, and biochemical assays.

In vivo techniques have also been developed targeting the interaction of biomaterials and leachables with different tissues or organs. For those in contact with the skin, eye, or mucosa, assays include:

- Sensitization and irritation assessed through visual observation, quantitative prediction of mutagenicity in Ames test (QPMT), and local lymph node assay (LLNA).
- Cytotoxicity evaluated with (immuno)histology.
- Genotoxicity, including micronucleus (MN) assay and peripheral blood MN assay.

To evaluate the effect of a biomaterial of a medical device that is in contact with blood, hemolysis, blood coagulation, plasma protein absorption, platelet adhesion, complement activation (monitored visually), spectrometry, ELISA, SEM, and platelet staining, may be used.

For implantable biomaterials and medical devices assessment could involve:

- Endothelization, necrosis, fibrous encapsulation, immune responses via histology, histochemistry, and immunochemistry.
- Immune response quantified using flow cytometry.
- Cytokine levels measured through mRNA and protein expression.
- Pyrogenicity tested with rabbit pyrogen tests.

Systemic effects are often monitored via techniques that detect leachables in blood using inductively coupled plasma mass spectrometry (ICP-MS), ICP-optical emission spectroscopy (OES), and HPLC. In addition:

- Hematopoiesis is analyzed via blood-cell assessment.
- Distal organ alterations can be observed macroscopically or through (immuno)histological methods.
- Teratogenicity and effects on reproduction are assessed via genetic characterization of gametes, sperm motility, ovule morphology, and implantation issues.

Embryonic development is evaluated using histology, immunohistochemistry, and macroscopic embryo assessment.

The definition of biocompatibility proposed here sufficiently addresses the practical problems of ground-level text mining for algorithm training. Our definition offers a robust foundation for tackling the pragmatic challenges encountered in the field. Endowed with explicit and well-defined attributes that are indispensable for the identification and evaluation of biocompatibility in diverse materials and their corresponding applications, it will be used in the context of training algorithms. However, it still leaves us with crucial gaps that the scientific community should address in the future.

Concluding remarks and future perspectives

From its inception, the concept of biocompatibility has been intimately linked to the very essence of the definition of biomaterials. The analysis of the definitions used by the scientific and clinical community has shown that the concept of biocompatibility is approached from a holistic perspective, attempting to capture both safety and functional aspects. In this sense, we could say that biocompatibility is what makes a material a biomaterial insofar as it is safe and fulfills its function adequately. Nonetheless, this ambitious definition, aiming to encompass the absence of adverse effects and sufficient functionality, is very vague. This poses a major challenge when striving for an unambiguous assessment of materials (see Outstanding questions). Unlike other

Outstanding questions

What is the best way to interpret and define host response in a biological system?

Should it focus only on *in vivo* data output, or should it encompass all *in vitro* studies?

Is the lack of undesirable effect (e.g., inflammation, immune response) sufficient to determine that a material is biocompatible?

What level of adverse effects sets the threshold of nonbiocompatibility and what should be an appropriate timeframe for their evaluation?

Should biocompatibility be defined or scaled differently for implantable versus nonimplantable materials and devices?

Is it necessary to have a specified material characterization as a precondition for scaling up biocompatibility?

Should any biomaterial used in a clinical setting (e.g., a 3D printed prosthesis, a stent, etc.) be considered a medical device or part of it, to simplify definitions?

Should we consider only the implantable medical devices or all that are in contact with tissue?

How do we include clinical data in the definition?

How do we correlate appropriate host response with biomaterial/medical device application/implantation?

Finally, can we establish a composite definition that associates all these attributes in a standardized manner?

Table 1. Summary of biocompatibility definitions

Definition	Strengths/advantages				Redundancies/limitations				Year	Refs
	Employed by		Addresses		Definition		Devices			
	ISO	FDA	*In vivo*	*In vitro*	Clear	Ambiguous	Implantable	Human host		
Biocompatibility is defined as the ability of a material to perform with an appropriate host response in a specific application	Yes	Yes	Yes	No	No	Yes	Yes	Yes	1987	[36]
Biocompatibility is defined as the capability of a finished and sterilized medical device to perform within an acceptable biological reaction in a clinical application (e.g., skin, blood, bone, etc.)	No	No	Yes	No	No	Yes	Yes	Yes	2001	[37]
Biocompatibility is defined as the ability of a biomaterial, prosthesis, or medical device to perform with an appropriate host response in a specific application	No	No	Yes	Yes	No	Yes	Yes	Yes	2001	[38]
Biocompatibility is a property not only of a material, but also of a material interacting with its environment. The interactions among material, host, and function continue over time; therefore, the biological response to a material is an ongoing process	No	No	Yes	No	No	Yes	Yes	Yes	2001	[39]
Biocompatibility may be formally defined as the ability of a material to elicit an appropriate biological response in a given biological application	No	No	Yes	No	No	Yes	Yes	Yes	2002	[40]
Biocompatibility is an ability of a material to perform its desired function without causing any local or systemic adverse response in the recipient of the material	No	No	Yes	No	No	Yes	Yes	Yes	2009	[41]
Measurements validating biocompatibility are usually either: (i) 'an assessment of the substances that leach from the biomaterial or device and their effect on living cells or organisms', or (ii) 'A measurement of the biological response to the biomaterials or device upon implantation in a living organism'	No	No	Yes	Yes	No	Yes	Yes	Yes	2011	[7]
Biocompatibility is the ability of an implant material to function *in vivo* without eliciting detrimental local or systemic responses in the body	No	No	Yes	No	Yes	No	Yes	Yes	2011	[7]
Biocompatibility is the ability of a material to locally trigger and guide normal wound healing, reconstruction, and tissue integration	No	No	Yes	Yes	Yes	No	Yes	No	2015	[42]
Biocompatibility evaluation of biocomposites strongly depends on various factors, including (i) materials type, (ii) structural and functional characteristics of the materials, (iii) manufacturing methodologies, (iv) sterilization techniques, (v) nature of contact with cells or tissues, (vi) potential interferences between the cell and the host, and (vii) linearity, sensitivity, and reproducibility of the assay, etc. Biocompatibility evaluation standardizes whether a material 'provokes considerable harmful or adverse effects'	No	No	Yes	Yes	No	Yes	Yes	Yes	2017	[34]
Biocompatibility is a complicated process depending on various factors. This process includes biofunctionality, bioinertia, bioactivity, and biostability. Biocompatibility leads to the surrounding tissue and the human body accepting the synthetic implants without any undesirable immunity response, allergic reactions, inflammatory or chronical problems, and, moreover, biocompatible mate rials are not carcinogenic	No	No	Yes	Yes	Yes	No	Yes	Yes	2019	[35]
Biocompatibility leads to the surrounding tissue and the human body accepting the synthetic implants without any undesirable immunity response, allergic reactions, inflammatory or chronic problems, and not being carcinogenic	Yes	No	Yes	No	Yes	No	Yes	Yes	2019	[35]

Table 1. (continued)

Definition	Strengths/advantages				Redundancies/limitations				Year	Refs
	Employed by		Addresses		Definition		Devices			
	ISO	FDA	*In vivo*	*In vitro*	Clear	Ambiguous	Implantable	Human host		
Biocompatibility is a term used to describe the capability of an implanted prosthesis to exist in harmony with surrounding tissues	Yes	Yes	Yes	No	No	Yes	Yes	Yes	2019	[43]
Biocompatibility strongly depends on the type of the application. The basic factors that influence biocompatibility are: (i) interaction with the surroundings, (ii) period of the implant application, (iii) surface biocompatibility, (iv) structural biocompatibility, (v) function, (vi) proportion, and (vii) material	No	No	Yes	Yes	Yes	No	Yes	Yes	2019	[35]
Biocompatibility concerns the phenomena that occur within the interactions between biomaterials and human patients, which ultimately control the performance of many facets of medical technology	No	No	Yes	No	No	Yes	Implantable and nonimplantable	Yes	2023	[4]
Biocompatibility is the evaluation of how therapeutic non-drug materials (implanted, inhaled, or surface contacting) interact with the human body, most often when in use as a medical device	No	No	Yes	No	No	Yes	Implantable and nonimplantable	Yes	2023	[44]

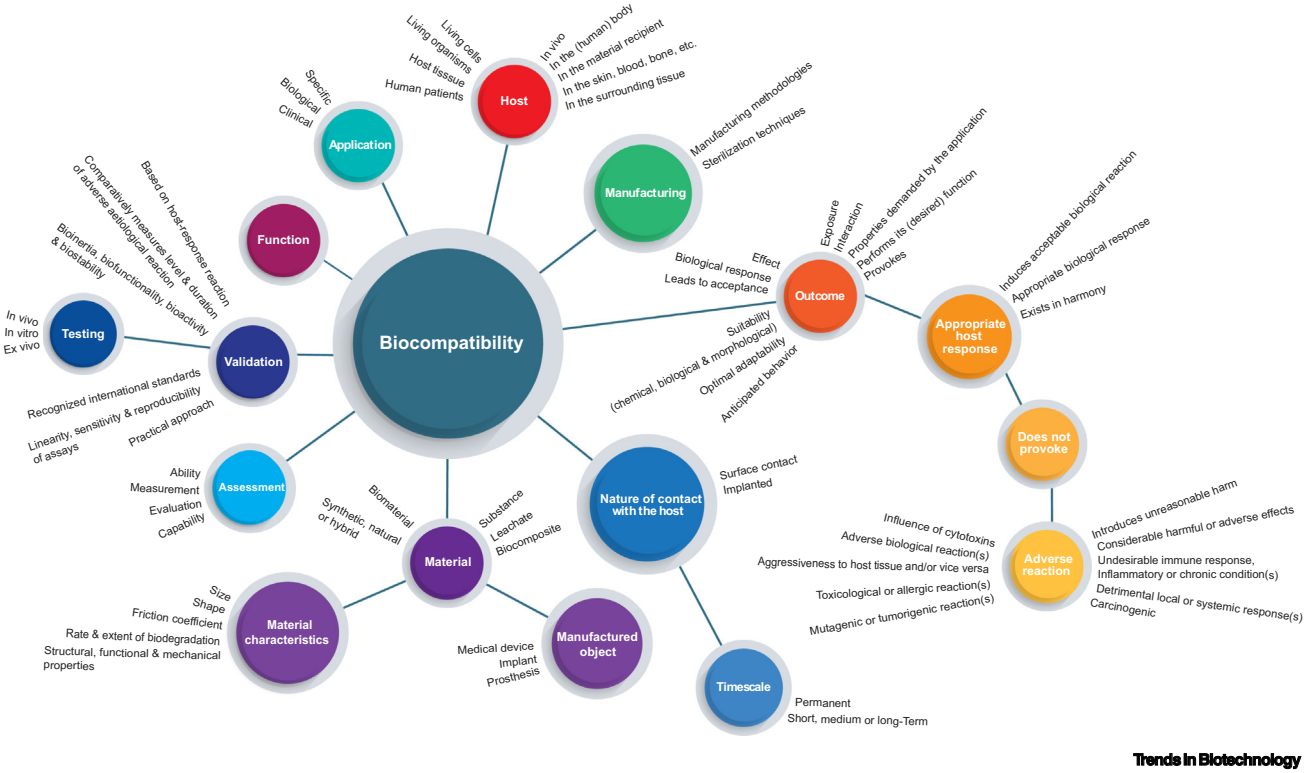

Figure 5. Road map used in this work to propose an integrated definition of biocompatibility. The methodology employed to establish a comprehensive biocompatibility definition is showcased using a conceptual diagram. This term diagram incorporates the key elements that collectively constitute the term and make up the revamped definition.

properties in various disciplines, which are often measurable and quantifiable, biocompatibility presents unique difficulties, convoluting the task of its definition.

This limitation becomes especially evident when it comes to applying data mining techniques to retrieve information on biocompatibility in a consistent and reliable way. There is a need for a definition that is perhaps less ambitious but clearly identifiable and measurable. Within this scope, it is necessary to dissociate the two aspects that are generally addressed in biocompatibility: safety and functionality. Rather, focusing on redefining biocompatibility as the absence of adverse effects would perhaps be more adequate. This redefinition is necessary to establish more objective criteria to determine vocabularies and classify data types identified by computational tools.

This would be a first step towards building well-structured and controlled vocabularies, which are indispensable for harnessing the enormous potential of AI techniques. Also, it could provide the necessary framework to scale adversity in the context of biocompatibility and establish uniform biocompatibility criteria, both of which are crucial for maintaining consistent standards for healthcare provision or regulatory purposes and preventing undue risks to patients or users. These would significantly contribute towards safety assurance and risk management, both for regulatory bodies' medical product safety assessment and for the public's trust. Furthermore, defining uniform biocompatibility scaling criteria would assist global trade regulatory alignment and enable post-market surveillance.

Overcoming the challenge of assigning quantitative units to biocompatibility would require multimodal and rigorous approaches, combining quantitative metrics and qualitative observations that can be adapted to emerging methodologies. These approaches should always consider the complexity of biological systems and the multifactorial nature of biocompatibility itself. Thus, to address this challenge, standardized testing protocols should be established, utilizing metrics and units where applicable. International standards such as ISO 10993 provide guidelines for conducting biocompatibility tests, while metrics like percentage of cell viability, cytokine concentrations (picograms per milliliter), biomarker expression levels, and tissue integration (millimeters) offer quantitative data. Dose–response studies could determine acceptable thresholds and dose-related quantitative units, while statistical methods could propose correlations between material properties, exposure levels, and biological responses. Additionally, long-term studies could assess delayed or chronic biocompatibility responses quantifying the effects over time.

Finally, advanced *in vitro* models – such as microfluidic devices and sensors, organ-on-a-chip systems, and 3D cell cultures – offer opportunities for precise measurements. These advances could address, at least partially, ethical concerns derived from the use of animal models as they have the potential to substitute these. As such, by utilizing big data and ML algorithms, large datasets can be mined and used to identify quantitative patterns and develop predictive models related to biocompatibility. These, however, should be continuously refined based on new research findings, emerging technologies, and feedback from regulatory bodies.

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Declaration of Interests

The authors declare no conflicts of interest.

Resources

[i]https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02017R0745-20230320

[ii]www.fda.gov/medical-devices/biocompatibility-assessment-resource-center/basics-biocompatibility-information-needed-assessment-fda

[iii]https://ncithesaurus.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary=NCI_Thesaurus&version=21.06e&ns=ncit&code=C63294&key=n819091014&b=1&n=0&vse=1

[iv]www.fda.gov/media/142959/download

[v]www.mckinsey.com/industries/life-sciences/our-insights/what-are-the-biotech-investment-themes-that-will-shape-the-industry

[vi]www.mckinsey.com/industries/life-sciences/our-insights/capturing-the-value-of-good-quality-in-medical-devices

[vii]www.theguardian.com/business/2022/sep/12/johnson-johnson-reaches-300m-settlement-over-pelvic-mesh-implants

[viii]https://cbit.bmt.tue.nl/

[ix]http://biomatdb.eu

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