Indian Journal of Biochemistry & Biophysics
Vol. 59, April 2022, pp. 431-439

A Review

Nanoinformatics - A newly introduced tool for research

Vibha Gulyani Checker[#], Bhavana Sharma[#] & Renu Kathpalia*

Department of Botany, Kirori Mal College, University of Delhi, Delhi-110 007, India

Received 16 December 2021; *revised 11 February 2022*

Research in the field of nanotechnology has witnessed rapid increase in the synthesis of Engineered nanoparticles (ENPs). This has even led to development of new discipline of Nanotoxicology. Advances in the field of Nanotoxicology further led to development of new domain-nanoinformatics. This new domain of nanoinformatics provides a computational perspective to biology and nanotechnology addressing multi level integration. Nanoinformatics not only helps in predicting nanoparticle structure, composition and behaviour but also covers raw data management, analysis of data derived from biomedical applications and simulation of nanoparticle interactions with biological systems. In addition, it accelerates nano-related research and applications into clinical practice. There are various computational models developed to study the key steps in nano-medicine like drug encapsulation and release, nanoparticle targeting, delivery and uptake and nanoparticle effects on cells and tissues. These prospects have opened up a large domain enabling possibilities of nanomedicine and frontiers for clinical practice and biomedical research in a cost-effective manner along with various applications including studies in clinical trials, toxicity assays, drug delivery systems. This review highlights new approaches for Engineered nanoparticles (ENP) risk assessment and regulation.

Keywords: Computational methods, Drug delivery system, Engineered nanoparticles (ENP), Nanoinformatics, Nanotoxicology, Risk assessment

Introduction

Nanoparticles (NPs) have wide applications in diverse fields and therefore there is an exponential increase in number of studies involvedusing the nanoparticles[1]. Last few years have seen an increase in the synthesis of engineered nanoparticles (ENPs) on an average of $10\text{-}10^5$ tons per year[2]. Even the global market of nanoparticle-based products[3] indicatethe same fact. Although, the unique properties of nanomaterials hold promise for many applications, but at the same time it also raises safety concerns for human health. These ENPs exhibit the ability to penetrate the human cells and flow in bloodstream which may lead to undesirable effects on the metabolic systems[4]. ENPs can exert their toxic effects by interacting directly with DNA or other biomolecules as they enter the cells *via* penetration through cell membrane[5]. The damaging effects of ENPs were also observed on plant organs, changing the length of stem, root and affecting plant growth. Many reports have documented the effects of ENPs through food chain revealing toxicity in the ecosystem[6]. Hazardous properties of nanoparticles depend on particle size, surface area, surface chemistry, crystalline structure, aggregation in media, and purity of these NPs. The risk profile of these nanoparticles is becoming challenging and precarious taking their life cycle into consideration. Unexpected results further add to the challenges of risk assessment as they may lead to serious miscalculations. Enthusiastic research on nanoparticles led to their revolutionary usage without prior knowledge about their behavior and prospective toxic effects. Insurgent usage of nanoparticles can be alarming for human health[2]. It is imperative to check biological effects of nanoparticle-based products on human health and environment from production, transportation, and recycling till disposal.

The main concepts on nanotoxicology were developed around 2004[7] for careful evaluation regarding sustainability and risk production of nanoparticles. There are two main strategies for toxicological evaluation: a) To test every single type of nanoparticle produced b) Predicting nanoparticle behavior with regard to its structure and composition[8]. Assessing the safety of nanoparticles through experiments is time consuming, therefore, computational methods offer a better alternative. The predictive modelling of nanoparticle risk assessment

---

#Equal first author

*Correspondence:

E-mail: rkathpalia@kmc.du.ac.in

is a reliable, comprehensive tool that is capable of predicting harmful influence of nanoparticle on environment and as well as on humans. Nanoinformatics emerged as a sub-branch of informatics to cater the aforementioned challenges *via* implication of systematic methodology and arrangement of raw data. It is described as “the science and practice of development of computational tools for implementing in nanoscale science. It involves development of functional mechanisms for collection, validation, storage, sharing, analysis, modeling and application of respective information”. This fascinating branch of science is still in its infancy, lack compiled literature and complete data from single source. Therefore, the aim of this review is to compile the strategies, tools used in nanoinformatics with a focus on their applications and challenges.

Nanoinformatics: An efficient tool for nanotoxicity assessment and data management

Research over the last decade, has shown impressive advancement in nano as well as biotechnology. Nanotechnology, which was introduced by Richard Feynman in 1979[9] has adopted many strategies in the past and developed into the advanced technology. In 1985, first nanomaterial for biomedical uses were designed and the term nanomedicine was widely used since 2004[10]. However, recently the understanding of physical and chemical properties of nanomaterials has gained momentum. To visualize, design, model and simulate nanomaterials and nanoparticles such as dendrimers, metallic nanoparticles, nanocapsules, nanospheres and quantum dots (QDs) computational chemistry, a powerful tool was used. Owing to their distinct chemical, magnetic and physical properties, NPs are desirable for various biomedical applications like targeting specific cell types, improving pharmacokinetics or bioavailability, and enhancement of signal detection, cancer therapy[11-15]. However, a slight variation in their physicochemical properties may change the composition and characteristic of these nanoparticles and add to their toxicity. It is of utmost importance to understand the biological and toxicological properties of nanomaterials to check whether the products are safe or not. Toxicological and ecotoxicological assays of different NPs is crucial in identifying the risk assessment in nanotoxicology (Fig. 1). Comprehensive *in vitro* and *in vivo* studies have revealed an initial understanding of the toxic mode of action of various nanoparticles. However, prediction of risk assessment and functioning of nanoparticles remains key challenges in development of efficient nanoparticle therapeutics.

Understanding the complexity of biological responses is necessary for regulation of novel nanomaterials. Diverse techniques like Transmission electron microscopy (TEM), Scanning electron microscopy (SEM), X-ray diffraction (XRD), Fourier transform infra-red spectroscopy (FTIR) are widely used for experimental validation of the size, shape, and structure of different NPs. Recently, amalgamation of various biological tools including the combined omics has been found helpful in accurate validation of NPs. However, these *in vitro* and *in vivo* methods for assessing the safety of novel nanomaterials are costly and laborious. On the contrary, computational or *in silico* analysis of nanoparticle risk assessment could become a trust-

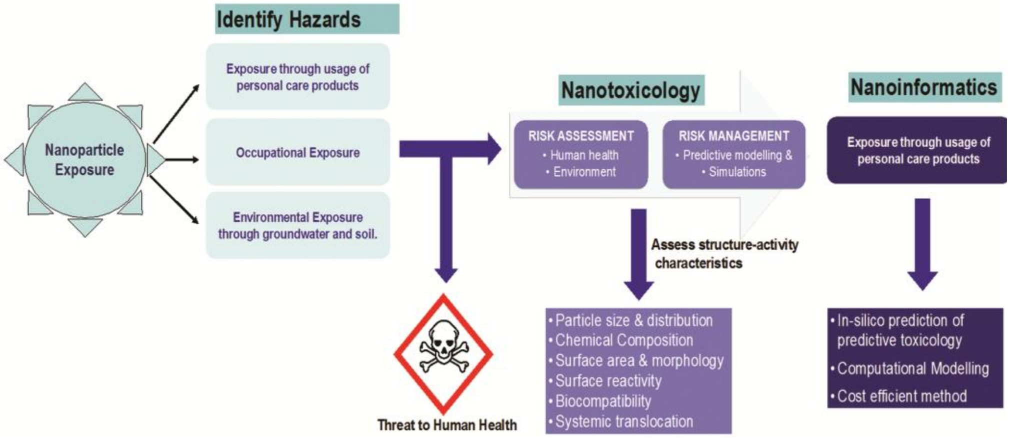

Fig. 1 — The role of nanoinformatics in *in silico* predications of nanotoxicology and development of computational tools for implementing in different field of nanoscale science. This frontier of science will be a boon for nanotechnology mainly tackling issues of nanotoxicology

worthy, convenient, affable and economical tool for analyzing the toxicity of NPs on the environment and humans[8]. *In silico* approaches may complement the experimental toxicity studies to potentially minimize the need for animal testing, reduce the cost andtime of toxicity tests and improve toxicity predictionand safety assessment. Additionally, the technique would be advantageous in estimating thenanotoxicity even before their synthesis[16].

Extensive research in the area of nanotechnology as well as informatics and nanotoxicological studies have generated bulk information/data on the structure, properties and effects of NPs. For successful and efficient management of this huge raw data, new informatics tools are required to archive, access, or annotate the relevant information and also to couple the curated information efficiently with other computational methods[17]. Latest advancements in precision of computational methods (like data mining, knowledge, discovery, modeling and simulation) have enabled effective tools to systematize the extraction, management, and storage of the huge data. Still, a significant issue with these methods is to find, access and share the data. Nevertheless, nanoinformatics provides a better, cost and time effective alternative for nanotechnology-information management and addressal of the aforementioned issues. Novel discipline of nanoinformatics like Investigation Study Assay tab-delimited format (ISA-TAB-Nano), Cancer Nanotechnology Laboratory (caNanoLab) and Nanomaterial Registry addresses the information challenges related to nanotechnology research. These databases allow data sharing and creation of data standards and, as the nanomaterial information progresses, it will provide innovative ways to develop tools specific to address the challenges at nanolevel[18].

Risk assessment through nanoinformatics

Emphatic areas in nanoinformatics includes (1) management of nano-data, (2) expansion of nano database, (3) providing nano-data curation, (4) evaluation of nano-data information, (5) literature mining for collection and meta-analysis, (6) data mining *via* development of quantitative structure–activity relationships (QSARs), (7) simulation studies on nanomaterials, their interactions with biological entities, and 8) risk assessment of NPs on environmental and human health[19].

Nanoinformatics is burgeoning at a rapid pace and provides data driven elucidationsfor designing safe nanomaterials. The functional fundamental platform for the processing of nano-safety assessment is provided by the validated and experimental data set[17]. The simplified schematic framework of nanoinformatics involved in synthesis of nanomaterial and their risk assessment is shown in (Fig. 2).

The broad strategies followed for retrieval of raw datasets and development of prediction models at nano-levels are (1) Collection and storage of experimental (NP characteristics) and reference material data, (2) Data curation and designing of molecular descriptors for standardization of information. (3) Data mining and simulation tools for generation of prediction models. (4) Validation of the obtained results by subject experts for safety assessment and further designing. (5) Finally, interpretation of models and linkage to education portals or external resources for development of Nano-databases[20,21].

In silico toxicology assessment of nanoparticles covers diverse computational tools including (Fig. 3): (1) databases to allow storage of the information on nanomaterials like their toxicity, and characteristics; (2) the multitude of soft-wares for generation of

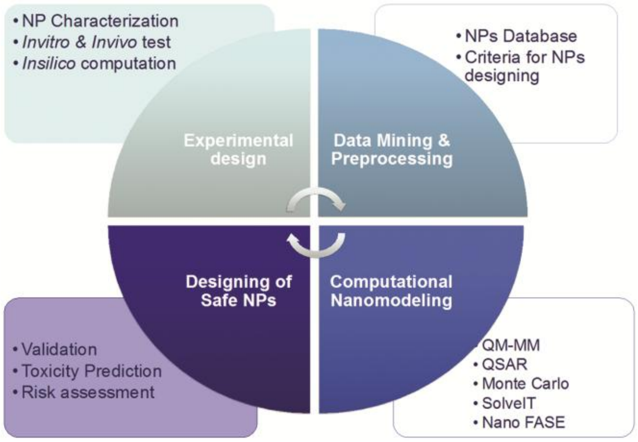

Fig. 2 — Schematic nanoinformatics framework broadly involving designing of safe NPs, designing experiments to characterize NPs, data mining as well as preprocessing and computational nanomodeling

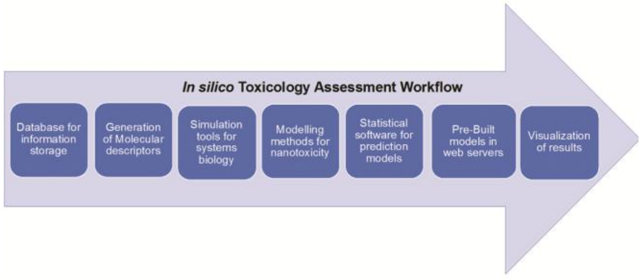

Fig. 3 — The computational workflow involving different steps for *in silico* toxicology assessment

molecular descriptors or ontologies; (3) simulation tools for systems biology and molecular dynamics; (4) modeling systems for prediction of toxicity; (5) computational tools like statistical packages and software for creation of prediction models; (6) skilled wizards like pre-built models in the servers for prediction oftoxicity; and (7) numerous visualization tools[21]. The various tools and resources available for nano-data analysis are enlisted in (Table 1).

Machine learning tools are widely used while designing the experiment for *in silico* prediction of toxic intermediates and end-points. Computational nanomodelling gives the opportunity to amalgamate the information available in different resources. Computational algorithms have the potential to provide the opportunity to the researcher to gain prior knowledge about physio-chemical properties, degradation, transformation, environmental fate, material safety of potential nanoparticles further advancing the practice of risk assessment of nanoparticles[8]. Development of machine learning and computational tools for risk assessment will pave the way regarding awareness about all stages of life cycle of hazardous nanoparticles and this will surely be a boon for legislators.

Table 1 — List of tools and resources available for nano-data analysis

Role	Resources
Data Collection	MinChar - Minimum Information for Nanomaterial Characterization Initiative
Data storage	MICAD - Molecular Imaging Contrast Agent Database
	NCL - Assay Cascade Protocols
	CaNanoLab - Cancer Nanotechnology Laboratory
	NBI KB - Nanomaterial-Biological Interactions Knowledgebase
	CSN- Collaboratory for Structural Nanobiology
	NIL - Nanotechnology Information Library
	OECED - OECD Database on Research into the Safety of Manufactured Nanomaterials
	ICON EHS - Nano-EHS Database Analysis Tool
Data exchange and standardization	ISO TC229 - Technical Committee229 Nanotechnologies
	NIST - National Institute of Standards and Technology Nanotechnology Portal
	ANSI - American National Standards Institute's Nanotechnology Standards Panel
Knowledge representation	NPO - NanoParticle Ontology
	NIO - Nanotech Index Ontology
Collaborative portals	SafeNano Nanotechnology Hazard and Risk
	Internano Information clearinghouse for the nanomanufacturing community
	NSTI Continuing education programs, scientific and business publishing and community outreach
	IEEE Theory, design, and development
Modelling and simulation	NanoHub - Analytical tools and simulations

Advances in nanoinformatics led to the development of robust and validated algorithms like neural networks, random forest, Nano-QSAR, Baysian network. These algorithms help in toxicity assessment of nanoparticles. Algorithms using simple regression models have also been developed and are widely used. In order to find correlation for the molecular structure, it is converted to a numerical matrix which describes the molecule mathematically. A lot of molecular descriptors are available which can transform this chemical information to a numerical system. Furxhi and his group[22] did vast analysis on machine learning computational tools which help in predicting toxicity. Though the complexity and heterogeneity of nanoparticles makes this conversion of molecular descriptors difficult and tricky, this approach is applicable and efficient following the FAIR (Findable, Accessible, Reuseable, Interoperable)[23] principles of nanosafety data. Nanoinformatics has become intrinsic to nanotechnology and a sequence of papers provide progressive insights into the state of art of nanoinformatics in risk assessment[24-29]. These studies provide informatic approaches for profiling nanomaterials for their adverse effects and aim for bridging the knowledge gaps for safe and sustainable use of nanomaterials. They also aid in providing *in vivo* datasets for adverse effects of nanomaterials.

Thrust areas of nanoinformatics

Nanotoxicology is amongst the major challenge faced by nanomedical technology where the harmful effects and the toxicity mechanisms of these nanomaterials are identified[30]. Owing to their toxicity these nanomaterials could not be utilized for biomedical purposes. These challenges in nanotechnology require tools and databases of nanoinformatics[18]. Natural, semi-synthetic and synthetic polymeric nanomaterials (PNPs) are used to incorporate the active pharmacological components to produce these nanoscale drug carriers. These are biodegradable, biocompatible with tissues, non-toxic, have a longer circulation time and broad therapeutic payload with few adverse effects. The efficiency of the drug delivery system is enhanced owing to the adjustable physical, chemical, and biological properties of PNPs that allow simultaneous delivery of multiple drugs with great specificity. PNPs are promising candidates for vaccine delivery, cancer therapy, antibiotic delivery, nucleic acids, proteins, and diagnostic agents with accuracy. PNPs may be useful in overcoming pharmacological drawbacks, such as limited solubility, low stability and excessive drug dosage, which restrict full potential of a drug. Extensive analysis of physicochemical properties like size, shape, and charge of ENPs may lead to generation of well-defined nanomaterials. Therefore, there is an urgent need for development of different informatics tools and techniques for augmentation of basic research *via* amalgamation of knowledge from clinical and experimental data. Artificial neural networks have been widely used to study factors controlling nanoparticle size and researchers found that polymer concentration affects size of polymer-based nanoparticles[31]. For characterization of size and encapsulation efficiency of nanomaterials, artificial neural networks were used by Shalaby and his co-researchers[32]. Nanoinformatics has also been used to find novel candidates for drug discovery[33] and paved the way to streamline the process of drug storage as prediction of drug leakage using computational models[34]. Load and leak models were used to screen molecular databases for screening candidates for drug delivery. To analyze the cellular uptake of nanoparticles various regression models (kNN based) have been exercised[35]. Nanoinformatics tools have also been used to study biological effects of targeted nanoparticles. There are examples citing the significance of computational algorithms in all stages of nanotechnology starting from preparation process, data analysis, prediction of particle properties and biological outcomes. Nano-QSR models are proposed for risk assessment of pesticides[36]. Progression of additional tools will lead to more systematized, automated, and digitized shift from trial-error based hit discovery of drugs[37]. Nanoinformatics opportunities in nanomedicine are listed in (Fig. 4).

Agricultural nanotechnology is indispensable part of food industry. Nanoformulations are in great usage for sustainable agriculture[38,39]. Theoretically, there can be direct release of nanoparticles in the environment which can significantly increase the incorporation of nanomaterials in the food-chain. Regulatory guidelines are required for understanding its impact on next generation risks emerging from agro-nanotechnology. This requires smart next-generation strategy for systemic utilization of nanoparticles as well as innovative assessment of risks emerging through this technology[40]. Nanoinformatics has imminent new-age potential to revolutionize modern agricultural practices. The major challenge in the agro-informatics sector is to include automation and computation at every step. Data-mining will play a dynamic role in this sector in a manner similar to nano-medicine.

Pay-off of nanoinformatics

The quantity of statistical data of nanoparticle toxicity is expanding day by day, suggesting that characteristics of these nanoparticles may control the impact of its adverse effects. Previous studies have shown that different shape, size, type and mode of usage of these nanoparticles have diverse impacts. Nanoinformatics approaches for nanosafety assessment, like analysis of nanomaterials characteristics, their interactions with biological, and cellular entities, transformation of nanomaterials, and their impacts are adding to data gap-filling, predictive modeling, and *in silico* tools for the risk evaluation of nanomaterials. Although, this emerging branch of science is still in its early stages but it has large benefits and impacts on all sectors of the society. Different aspects of nanoinformatics and its huge impact on international research are explained in (Fig. 5). These major areas have been broadly categorized into eight different sectors (1) industrial, (2) financial, (3) international collaboration, (4)

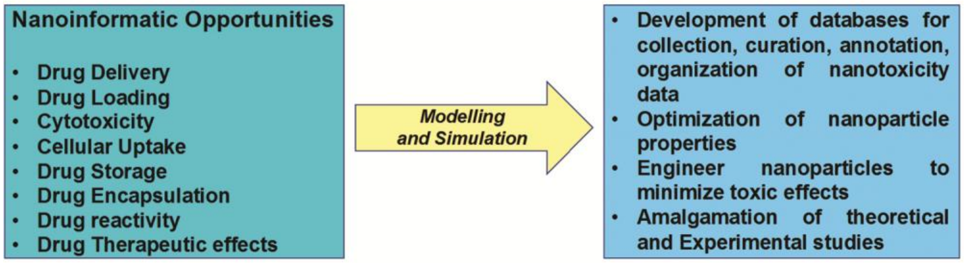

Fig. 4 — Nanoinformatics opportunities in different fields of nanomedicines. Further development of tools will shift this trial-error based hit discovery of drugs to a more organized, digitized and automated approach

Industrial
- New informatics techniques may allow companies and academic settings to work on nanotechnology and nanomedical research, without large budget

Economic
- Enormous financial importance with exponential growth of investment & revenues.

International Collaboration
- European groups can be funded by the US NIH and NSF for facilitating collaborative research and exchange.

National Policy
- Opportunities for new research programs might arise, linking directorates and people working in the involved areas.

Informatics
- There are challenges for linking BMI and nanoinformatics objectives, methods and tools that can be shared, exchanged and reused. Examples include databases, informatics tools, ontologies (biomedical and nano),services, etc

Societal
- Nanotechnology and nanomedicine have important associated issues like nanotoxicity (both animal and environmental) and also ethical, cultural, media, entertainment, philosophical and even religious aspects

Educational
- New academic programmes can be created or classical programmes – eg,BMI or medicine – can be expanded

Scientific
- New synergy between established disciplines like biomedical informatics and nanomedicine, leading to a new subdiscipline or area called Nanoinformatics.

Fig. 5 — List of different sectors influenced and benefitted by nanoinformatics (*ACTION-Grid White Paper*)[40]

national policy, (5) informatics, (6) societal, (7) educational, and (8) scientific[41]. Boom of Nanoinformatics has opened gates for expansion of various sectors as described by Maojo and his group[30].

Development of new informatics techniques in industrial sectors, may allow companies and academic platforms to work on nanotechnology and nanomedical research even with limited funding. Financial benefits could be provided by nanoinformatics sector *via* exponential growth of investment & revenues as well as by creating new job opportunities. Area of nanoinformatics has also created numerous educational and scientific prospects where development of new academic programs could be done along with expansion of classical programs. This novel branch of research has facilitated collaborative research and exchange of information between international research groups. With the progression of this branch of science, new opportunities may arise like development of new research programs and linking directorates under the National policy scheme. Earlier, there were issues in linking sharing and exchange of biomedical informatics with nanoinformatics including databases, informatics tools, ontologies (biomedical and nano), services. Also, nanotechnology and nanomedicine sectors may hold certain concerns including the nanotoxicity (human, animals and environment) as well as social, educational or religious aspects. Bringing the diverse research groups together under an umbrella may provide better addressal of these aspects. Thus, the novel synergy established between diverse disciplines including biomedical informatics and nanomedicine leading to a new subdiscipline called Nanoinformatics, may help in better addressal and outlook of the grey areas in nano-related issues[30]. Although, nanoinformatics has a huge scope in resolving future issues but at same time has bottlenecks and challenges which needs to be addressed for effective utility of this tool.

Challenges

Low quality of accessible information, in terms of its dependability and reproducibility represents a major challenge in nanoinformatics probably owing to different reasons, including:

- Scarcity of suitable tools for physicochemical characterization of nanomaterials.
- Absence of reference material to be utilized in the assays.
- Absence of curation and annotation of accessible information so that its reliability could be checked.
- Lack of accessible framework
- Gaps in the databases
- Absence of large mature datasets for designing of data infrastructure.
- Requirement of training materials for standard examines.
- Lack of integration of nanotechnology with omics and system biology data.

Furthermore, slow development of standardized ontologies, data sharing formats that permits user-friendly interfaces for diverse disciplines through a fit arrangement of concept definitions[30,42].

Grey areas in nanoinformatics to be addressed in future are shown in (Fig. 6). A major challenge with nanoinformatics is that in spite of being a supporting technology it should focus on amalgamation of different areas of basic research with translational research. A huge variety of nanomaterials cannot be utilized commercially due to lack of better characterization or validation method and informatics system availability to researchers for translating large chunk of raw information. These challenges suggest the dire need for informatics framework. Nanotechnology offers the desire for creating and testing these frameworks so that we can develop better techniques for extending them with continuously growing database. Thus, nanoinformatics methods and tools are critical for efficient handling of myriad of huge information resources, a basic challenge faced by researchers, clinicians, practitioners, and information brokers. In this sense, nanoinformatics could provide a platform to allow upgrading the information as well as enhancing the model reproducibility in research areas[30]. Educational and ethical aspects of nanomedicine will remain the central question for nanoinformatics. For growth of nanoinformatics, it is crucial that people from different scientific community and skills like informatics, medicine, science, and pharmacy should collaborate to carry out systemic studies.

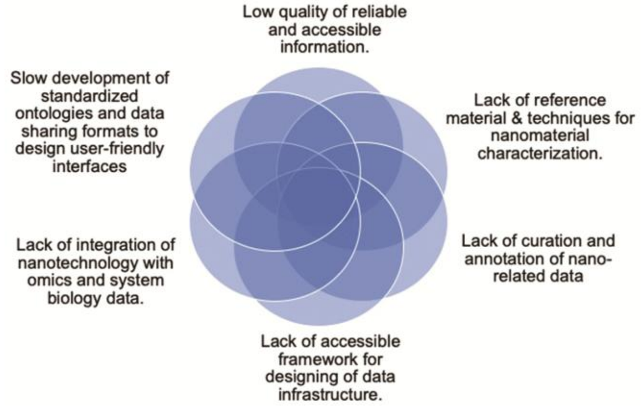

Fig. 6 — Grey areas in nanoinformatics which needs to be addressed in future

Outlook

Nanoinformatics has emerged out as the most significant functional tool to analyze the structure and physico-chemical properties of nanomaterials and engineered nanoparticles. The major contribution of this computational and statistical tool is in clinical diagnosis, drug delivery and their interaction with the environment in the application of nanomedicines. Nanoinformatics has catalyzed nanomedicines and has the potential to accelerate growth in other fields as well promising new exciting frontiers such as creating awareness at nanoscale. Nanoinformatics will help in functional discoveries of nanotoxicology to serve the need of stakeholders at each stage of nano value chain. Due to continuous expansion of nanotechnology and nanotoxicology research databases, the organization, storage, validation, analysis, and application of the retrieved data has become a herculean task. Nanoinformatics is facing numerous challenges and requires significant speculation to accelerate research in this field. There is emergent need for international research collaborations with expertise in computational modelling and simulations, nanotechnology and nanotoxicology. Astringent approach to foster effective nanoinformatics infrastructure will indeed bea boon for nanotechnology industry in near future.

Conflict of interest

All authors declare no conflict of interest.

References

1 Khan I, Saeed K & Khan I, Nanoparticles: Properties, applications and toxicities. *Arab J Chem*, 12 (2019) 908.

2 Al-Mubaddel FS, Haider S, Al-Masry WA, Al-Zeghayer Y, Imran M, Haider A, Zahoor & Ullah Z, Engineered nanostructures: A review of their synthesis, characterization and toxic hazard considerations, *Arab J Chem*, 10 (2017) 376.

3 Kathpalia R & Verma A, Bio-inspired nanoparticles for artificial photosynthesis. *Mater Today: Proc*, 45 (2021) 3825.

4 Aillon KL, Xie YM, El-Gendy N, Berkland CJ & Forrest ML, Effects of nanomaterial physicochemical properties on in vivo toxicity. *Adv Drug Delivery Rev*, 61 (2009) 457.

5 Shang L, Nienhaus K & Nienhaus GU, Engineered nanoparticles interacting with cells: size matters. *J Nanobiotechnol*, 12 (2014) 1.

6 Maharramov AM, Hasanova UA, Suleymanova IA, Osmanova GE & Hajiyeva NE, The engineered nanoparticles in food chain: potential toxicity and effects. *SN Appl Sci*, 1 (2019) 1.

7 Donaldson K, Stone V, Tran CL, Kreyling W & Borm PJA, Nanotoxicology. *Occup Environ Med*, 61 (2021) 727.

8 Pikula K, Zakharenko A, Chaika V, Kirichenko K, Tsatsakis A & Golokhvast K, Risk assessment in nanotoxicology: bioinformatics and computational approaches. *Curr Opin Toxicol*, 19 (2020) 1.

9 Feynman RP, There's plenty of room at the bottom. *J Microelectromech Syst*, 1 (1992) 60.

10 González-Nilo F, Pérez-Acle T, Guínez-Molinos S, Geraldo DA, Sandoval C, Yévenes A, Santos LS, Laurie VF, Mendoza H & Cachau RE, Nanoinformatics: an emerging area of information technology at the intersection of bioinformatics, computational chemistry and nanobiotechnology. *Biol Res*, 44 (2011) 43.

11 De Jong WH & Borm PJ, Drug delivery and nanoparticles: applications and hazards. *Int J Nanomed*, 3 (2008) 133.

12 Desai PP, Date AA & Patravale VB, Overcoming poor oral bioavailability using nanoparticle formulations – opportunities and limitations. *Drug Discov Today Technol*, 9 (2011) 87.

13 Biswas L, Shukla V, Kumar V & Verma A, Smart Drug-Delivery Systems in the Treatment of Rheumatoid Arthritis: Current, Future Perspectives. In: *Smart Drug Delivery* (Ed by Dr. Usama Ahmad. DOI: 10.5772/intechopen.99641, (2021).

14 Yadav M, Niveria K, Sen T, Roy I & Verma A, Targeting nonapoptotic pathways with functionalized nanoparticles for cancer therapy: Current and future perspectives. *Nanomedicine*, 16 (2021) 1049.

15 Mittal D, Biswas L & Verma A, Redox resetting of cisplatin-resistant ovarian cancer cells by cisplatin-encapsulated nanostructured lipid carriers. *Nanomed*, 16 (2021) 979.

16 Madan AK, Bajaj S & Dureja H, Classification models for safe drug molecules. In: *Computational Toxicology* (Ed by B Reisfeld & AN Mayeno, Humana Press, New York 930) 201399.

17 Maojo V, Martin-Sanchez F, Kulikowski C,Rodriguez-Paton A & Fritts M, Nanoinformatics and dna-based computing: catalyzing nanomedicine. *Pediatr Res*, 67 (2010) 481.

18 Panneerselvam S & Choi S, Nano informatics: Emerging databases and available tools. *Int J Mol Sci*, 15 (2014) 7158.

19 Liu R & Cohen Y, Nanoinformatics for environmental health and biomedicine. *Beilstein J Nanotechnol*, 6 (2015) 2449.

20 Iglesia DDL, Cachau RE, García-Remesal M & Maojo V, Nanoinformatics knowledge infrastructures: Bringing efficient information management to nanomedical research. *Comput Sci Discov*, 6 (2013) 014011.

21 Raies AB & Bajic VB, *In silico* toxicology: computational methods for the prediction of chemical toxicity. *Wires Comput Mol Sci*, 6 (2016) 147.

22 Furxhi I, Murphy F, Mullins M & Poland CA, Machine learning prediction of nanoparticle in vitro toxicity: A comparative study of classifiers and ensemble-classifiers using the Copeland Index. *Toxicol Lett*, 312 (2019) 157.

23 Lynch I, Afantitis A, Greco D, Dusinska M, Banares MA & Melagraki G, Editorial for the special issue from nanoinformatics to nanomaterials risk assessment and governance. *Nanomaterials*, 11 (2021) 121.

24 Ban Z, Zhou QX, Sun AQ, Mu L & Hu XG, Screening priority factors determining and predicting the reproductive toxicity of various nanoparticles. *Environ Sci Technol*, 52 (2018) 9666.

25 Choi JS, Ha MK, Trinh TX, Yoon TH & Byun HG, Towards a generalized toxicity prediction model for oxide nanomaterials using integrated data from different sources. *Sci Rep*, 8 (2018) 6110.

26 Rossi L, Bagheri M, Zhang WL, Chen ZH, Burken JG & Ma XM, Using artificial neural network to investigate physiological changes and cerium oxide nanoparticles and cadmium uptake by *Brassica napus* plants. *Environ Pollut*, 246 (2019) 381.

27 Kovalishyn V, Abramenko N, Kopernyk I, Charochkina L, Metelytsia L, Tetko IV, Peijnenburg W & Kustov L, Modelling the toxicity of a large set of metal and metal oxide nanoparticles using the OCHEM platform. *Food Chem Toxicol*, 112 (2018) 507.

28 Kinaret PAS, Ndika J, Ilves M, Wolff H, Vales G, Norppa H, Savolainen K, Skoog T, Kere J, Moya S, Handy RD, Karisola P, Fadeel B, Greco D & Alenius H, Toxicogenomic Profiling of 28 Nanomaterials in Mouse Airways. *Adv Sci*, 8 (2021) 2004588.

29 Gazzi A, Fusco L, Orecchioni M, Ferrari S, Franzoni G, Yan JS, Rieckher M, Peng G, Lucherelli MA & Vacchi IA, Graphene, other carbon nanomaterials and the immune system: Toward nanoimmunity-by-design. *J Phys Mater*, 3 (2020) 034009.

30 Maojo V, Fritts M, Iglesia DDL, Cachau RE, Garcia-Remesal M, Mitchell JA & Kulikowski C, Nanoinformatics: a new area of research in nanomedicine. *Int J Nanomed*, 7 (2012) 3867.

31 Asadi H, Rostamizadeh K, Salari D & Hamidi M, Preparation of biodegradable nanoparticles of tri-block PLA–PEG–PLA copolymer and determination of factors controlling the particle size using artificial neural network. *J Microencapsul*, 28 (2011) 406.

32 Shalaby KS, Soliman ME, Casettari L,Bonacucina G, Cespi M, Palmieri GF, Sammour OA & El Shamy AA, Determination of factors controlling the particle size and entrapment efficiency of noscapine in PEG/PLA nanoparticles using artificial neural networks. *Int J Nanomed*, 9 (2014) 4953.

33 Cern Y, Barenholz Y, Tropsha A & Goldblum A, Computer-aided design of liposomal drugs: In silico prediction and experimental validation of drug candidates for liposomal remote loading. *J Controlled Release*, 173 (2014) 125.

34 Cern A, Marcus D, Tropsha A, Barenholz Y & Goldblum A, New drug candidates for liposomal delivery identified by computer modeling of liposomes' remote loading and leakage. *J Control Release*, 252 (2017) 18.

35 Weissleder R, Kelly K, Sun EY, Shtatland T & Josephson L, Cell-specific targeting of nanoparticles by multivalent attachment of small molecules. *Nat Biotechnol*, 23 (2005) 1418.

36 Villaverde JJ, Sevilla-Moran B, Lopez-Goti C, Alonso-Prados JL & Sandin-Espana P, Considerations of nano-QSAR/QSPR models for nanopesticide risk assessment within the European legislative framework. *Sci Total Environ*, 634 (2018) 1530.

37 Hagit S, Shamay Y, Nanoinformatics in drug delivery. *Isr J Chem*, 60 (2019) 1108.

38 Fraceto LF, Grillo R, de Medeiros GA, Scognamiglio V, Rea G & Bartolucci C, Nanotechnology in agriculture: which innovation potential does it have? *Front Environ Sci*, 4 (2016) 20.

39 Kumar K, Dangi K & Verma A, Efficient & eco-friendly smart nano-pesticides: Emerging prospects for agriculture. *Mater Today: Proc*, 45 (2021) 3819.

40 Mittal D, Kaur G, Singh P, Yadav K & Ali SA, Nanoparticle-based sustainable agriculture and food science: recent advances and future outlook. *Front Nanotechnol*, 2 (2020) 10

41 ACTION-Grid Consortium. The ACTION-Grid White Paper: Linking Biomedical Informatics, Grid Computing and Nanomedicine. 2010. Available from: http://www.action-grid.eu/documents/ACTION-Grid%20White%20Paper.pdf. 2012.

42 Powers CM, Mills KA, Morris SA, Klaessig F, Gaheen S, Lewinski N & Hendren OC, Nanocuration workflows: Establishing best practices for identifying, inputting, and sharing data to inform decisions on nanomaterials. *Beilstein J Nanotechnol*, 4 (2015) 1860.