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Nanotechnology and Artificial Intelligence to Enable Sustainable and Precision Agriculture

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Abstract

Climate change, increasing populations, competing demands on land for production of biofuels, and declining soil quality are challenging global food security. Finding sustainable solutions requires bold new approaches and integration of knowledge from diverse fields, such as materials science and informatics. The convergence of precision agriculture, whereby farmers respond in real-time to changes in crop growth, with nanotechnology and artificial intelligence offers exciting opportunities for sustainable food production. Coupling existing models for nutrient cycling and crop productivity with nanoinformatics approaches to optimize targeting, uptake, delivery nutrient capture and long term impacts on soil microbial communities will allow design of nanoscale agrochemcials that combine optimal safety and functionality profiles.

Introduction

The Green Revolution, i.e. the 3rd Agricultural Revolution, which occurred between the 1950s and 1960s, dramatically increased global agriculture productions yield thereby avoiding the spread of famine and malnutrition. However, the world population has also grown by more than 5 billion since the beginning of the Green Revolution, entailing a continuous growth of crop production. The global agriculture and food security sector is facing a wide spectrum of challenges such as low crop yields, declining soil health and fertility, low use efficiency of agrochemicals due mainly to excessive use of fertilizes and pesticides, shrinking arable land *per capita* and diminishing freshwater availability for irrigation[1]. Moreover, climate change, as arising from increasing atmospheric CO_2 concentration leading to rising temperature, is likely to further affect the resilience of agricultural soils and their ability to sustain productivity and ensure food security for an increasing human population[2]. Nanotechnology offers great potential to enable precision and sustainable agriculture, the opportunities and challenges of which have been discussed in several recent reviews covering strategies to enhance crop nutrition and smart plant sensors[3, 4, 5]. Using nanotechnology, the delivery of fertilizer[6] can be tailored by targeting to specific tissues / organisms and stimuli-responsive release, as well as potentially improving nutrient use efficiency (NUE) by releasing the nutrient slowly for plant uptake[7]. Nano-enabled agriculture is expected to target pests more efficiently using lower amounts of pesticide[8] thereby avoiding widespread impacts on soil health and biodiversity, and improving soil function and nutrient cycling *via* soil microbiome enhancement (optimization of nitriying/denitrifying bacterial communities). Longer term applications include development of smart "sensor" plants, whereby the plant itself is adapted, using targeted delivery of nanomaterials (NMs), for sensing abiotic stress[9]. As with all new technologies however, the risks must be evaluated in parallel with the benefits, and indeed several NMs have been identified to cause negative changes in soil community structure, e.g, TiO_2 NMs cascading negative effects on denitrification enzyme activity and a deep modification of the bacterial community structure after just 90 days of exposure to a realistic concentration of NPs (1 mg kg^{-1} dry soil)[10], while studies with Ag NMs, which are well-known for their antimicrobial activity have shown that the extent of impact on soil community composition over 90 days are affected by exposure time and physicochemical composition of soil as well as the type and coating of the NMs[11]. Thus, an important caveat at the outset of this review is that NMs represent a very broad spectrum of chemistries, compositions and physicochemical properties, which are dynamic and evolving as the NMs interact with their surroundings, and as such generalisations regarding their applications in agriculture are difficult, and predictions of long-term effects are challenging currently.

However, as noted in the aforementioned reviews[3, 4, 5], the development of nanotechnology for agricultural applications is still at an early stage and is moving forward quite slowly. Significant differences may exist between nanotechnology-based pesticides and conventional pesticides, including altered bioavailability, sensitivity, dosimetry, and pharmacokinetics[12, 13]. Challenges and barriers include limited understanding of plant-NMs interactions, limited methods for efficient delivery of NMs to plants and soil, risks of potentially hazardous effects of NMs to human health from accumulation of NMs and active ingredient residues in edible portions of plants[4], and to long term soil quality and soil health from accumulation of NMs and their degradation products in soil and resultant potential alterations in microbial biodiversity[14]. There is an urgent need to address these barriers and achieve a true win-win scenario, whereby improved agricultural production, reduced environmental pollution from agriculture and lower costs for farmers can be achieved synergistically. A one-health approach to nano-agriculture was proposed by Lombi et al., that requires interdisciplinarity and the bridging of human and environmental health research[15]. Computational approaches including artificial intelligence (A.I.) and machine learning (M.L.) modelling will undoubtedly play critical roles in the progess of nano-enabled agriculture, and are already starting to gain regulatory acceptance for NMs safety assessment.

The application of computers and artificial intelligence (A.I.) in agriculture is not new – for example, articles addressing software for integrated resource management[16], image digitization for soil and crop science[16], and light and temperature monitoring and control for plants[17] were published 35 years ago! The rise of remote sensing and integration of remote sensing data into decision support tools for contemporary farming systems is expected to improve yield production and management while reducing operating costs and environmental impact[18]. Agricultural systems models have emerged over the last 50 years, spanning field, farm, landscape, regional, and global spatial scales and engaging questions in past, current, and future time periods. Integrated agricultural systems models combining grasslands and cropping models, livestock models, pest and disease models and risk behaviour models are also emerging, although data gaps exist across all aspects, hampering their implementation[19]. However, the comvergence of A.I. approaches and nano-enabled agriculture is in its infancy and as such the current perspective aims to stimulate the development of this important area.

The rapid pace of the development of nanotechnologies, the enormous diversity of physico-chemical properties of NMs and their dynamic interactions with, and transformations, by their surrroundings (e.g., corona formation, dissolution, sulfidation etc.[20, 21]) leads to the need for *in silico* approaches to predict and assess their safety[22]. Nanoinformatics is a powerful way of relating the nanostrucutural features with functional properties based on data-driven A.I. and M.L. approaches[22, 23, 24]. Nanoinformatics emerged a decade ago in the context that development and implementation of nanotechnology in the real world requires the harnessing of information at the nexus of environmental and human safety, risk assessment and management, physiochemical properties and function. With A.I. and M.L. enabled *in silico* risk assessment[25], NMs grouping and classification[26], and safe-by-design[27] NMs design, as well as for predictions of NMs corona formation[28] and consequences for cellular attachment and uptake[29, 30, 31], nanoinformatics has played significnt roles in the area of nanosafety and nanomedicine, while there is also ample scope of nanoinformatics in nano-enabled agriculture that has not been explored, including for prediction of NMs interactions with and impacts on rhizosphere secretions, NMs transformations before and during uptake and translocation, NMs impacts on soil microbial communities and for predictions up plant uptake following foliar application. Experimetnal data are emerging in all these areas[32, 33, 34], and a dedicated effort to integrate and curate this data, and present it in a format suitable for modelling is currently underway by the authors in the scope of their nanoinformatics e-infrastructure projects NanoCommons and NanoSolveIT[35]. Coupling these approaches with existing models for nutrient cycling[36], NUE[37] and crop productivity[38] and the aforementioned agricultural systems models into an overall Integrated Approach for Testing and Assessment (IATA) will allow co-optimisation of NMs for use in agricultural systems that combine safety and functionality profiles enabling precision agriculture.

In this perspective, emerging applications of nanotechnology and nanoinformatics in agriculture and gaps in current understanding are outlined. Key research areas are identified where the application of A.I. will support the effective implementation of nanotechnology in agriculture, with a view to enhancing productivity and protecting or improving environmental quality. Current applications of A.I. in agriculture, in nanotechnology broadly, and in nano-enabled agriculture are also outlined, along with identification of key areas where their convergence and integration can accelerate the development of sustainable nano-enabled precision agriculture.

Current challenges in agriculture

With an ever increasing human population under a decreasing per capita agricultural land globally[39], a key challenge is to optimize productivity whilst ensuring the conservation of soil health and the protection of environmental quality. Agrochemicals (fertilizers and pesticides) enabled an increase in productivity such that half of us are alive today due to the invention of industrial ammonia production and its use as a fertilizer globally. However, the intensification of agriculture for enhanced productivity resulted in extremely poor NUE globally (<50%)[40, 41]. Poor NUE under an excessive fertilizer use culture thus poses a serious threat to environmental quality as large amounts of nutrients are lost into water and air causing eutrophication and greenhouse effects. For example, agriculture contributes nearly 11% of global greenhouse gas emissions[42]. Nitrogen (N) and phosphorus (P) fertilizer use in agriculture is one of the main drivers behind the breach of the safe planetary boundaries for these elements that could trigger irreparable damage to the environment[43]. Rockstrom et al. recommended a reduction of reactive N use in agriculture from 150 Mt N y^{-1} to about 35 Mt N y^{-1} globally to ensure sustainability[43]. Such a reduction can only be achieved through a combination of approaches including targeted nano-enabled delivery of fertilizer to match plant demands to avoid excessive losses, development and availability of low-cost in situ nutrient sensing technology to help farmers plan fertilization efficiently, introduce rotations into agriculture to recover the health and fertility of soils, utilize farm yard manure and slurries for meeting nutrient demands and identifying crop breed that are efficient in nutrient uptake and even fixing atmospheric N_2 directly or thorugh enhance symbiosis are some of the key measures to enhance NUE, reduce excessive fertilization and the subsequent losses of reactive N from cultivated soil[44]. Unlike N, available terrestrial P reserves are non-renewable and the current losses of available P from agriculture to water (rivers and oceans) is 10 times the pre-industrial and agricultural intensification era[43]. This unsustainable use of P fertilizer in agriculture is thus posing a risk to global food security[45], while causing eutrophication of fresh and coastal water bodies, together with N[41].

The grand challenge in agriculture is therefore that of optimizing usage efficiences, timing and targeting of fertilizer use to enhance and sustain crop production and while simultaneously reducing amounts of fertilizers used and losses to environments external to agricultural catchments. While regulatory and voluntary fertilizer use policies in Europe and USA have resulted in reduction of losses to water, an overall enhancement in NUE was not achieved[46]. Recent efforts to enhance NUE include utilization of biofertilization to enhance microbial biodiversity[47], and application of a range of N management tools across the growing season including soil testing, plant tissue testing, spectral response, fertilizer placement and timing and vegetative indexes (leaf area index, and Normalized Difference Vegetation Index (NDVI)) through A.I. enabled drones, handheld sensors, and satellite imagery[48]. Rockstrom et al. suggested that substantial N and P fertilizer use reduction can protect the planet from breaching resilence thresholds, if such reductions can still ensure productivity[43].

Gobal agricultural yields are also impacted by crop loss due to competition from weeds, insect damage and plant diseases. Weed competition causes 34% of crop loss on a global scale, while microbial diseases and pest damage also cause 34% of crop loss [49]. The application of synthetic herbicides and pesticides thus increases yields (reduces crop loss) and, in the case of herbicides containing N, P and K, improves food quality through enhanced nutrient uptake and retention[50]; however, these agrochemicals, which are designed to kill, also cause severe adverse impacts on the health of human and non-targeted organisms and soil fertility, and result in contamination of water, soil and air[51]. Mis-use of agrichemicals on poor quality soils, soil degradation as a result of farming intensification, shrinking water availability and decreasing water quality, and globalization of diseases have led to low resilience of agriculture systems.[52] Moreover, climate changes such as elevated atmospheric CO_2 levels and increasing temperatures also potentially impact the future of agriculture.[53]

Nanotechnology applications in the agricultural sector have great potential to improve all aspects of crop production, that is, to increase crop production yields and resource use efficiency whilst reducing agriculture-related environmental pollution, thereby ensuring global food security whilst ensuring future agricultural sustainability. Coupling existing models for nutrient cycling and crop productivity with A.I. and machine learning to optimize targeting, uptake, delivery, nutrient capture and soil microbial composition will allow design of nanoscale agrochemcials that combine optimal safety and functionality profiles and implementation of nano-agrichemicals into mainstream agricultural systems management.

Current applications of nanotechnology in agriculture

Nanotechnology offers the benefit of reducing costs of fertilization at farm level directly and at global level, indirectly, through reduction in environmental damage and environmental clean up costs associated with agriculture-derived pollution. More importantly, enhancing NUE through nanotechnology application in agriculture is a promising intervention technology that could revolutionize and modernize agriculture making it precise and targeted. **Figure 1** summarises 4 key areas where nanotechnology is, and will continue to, improve the precision and sustainability of agriculture.

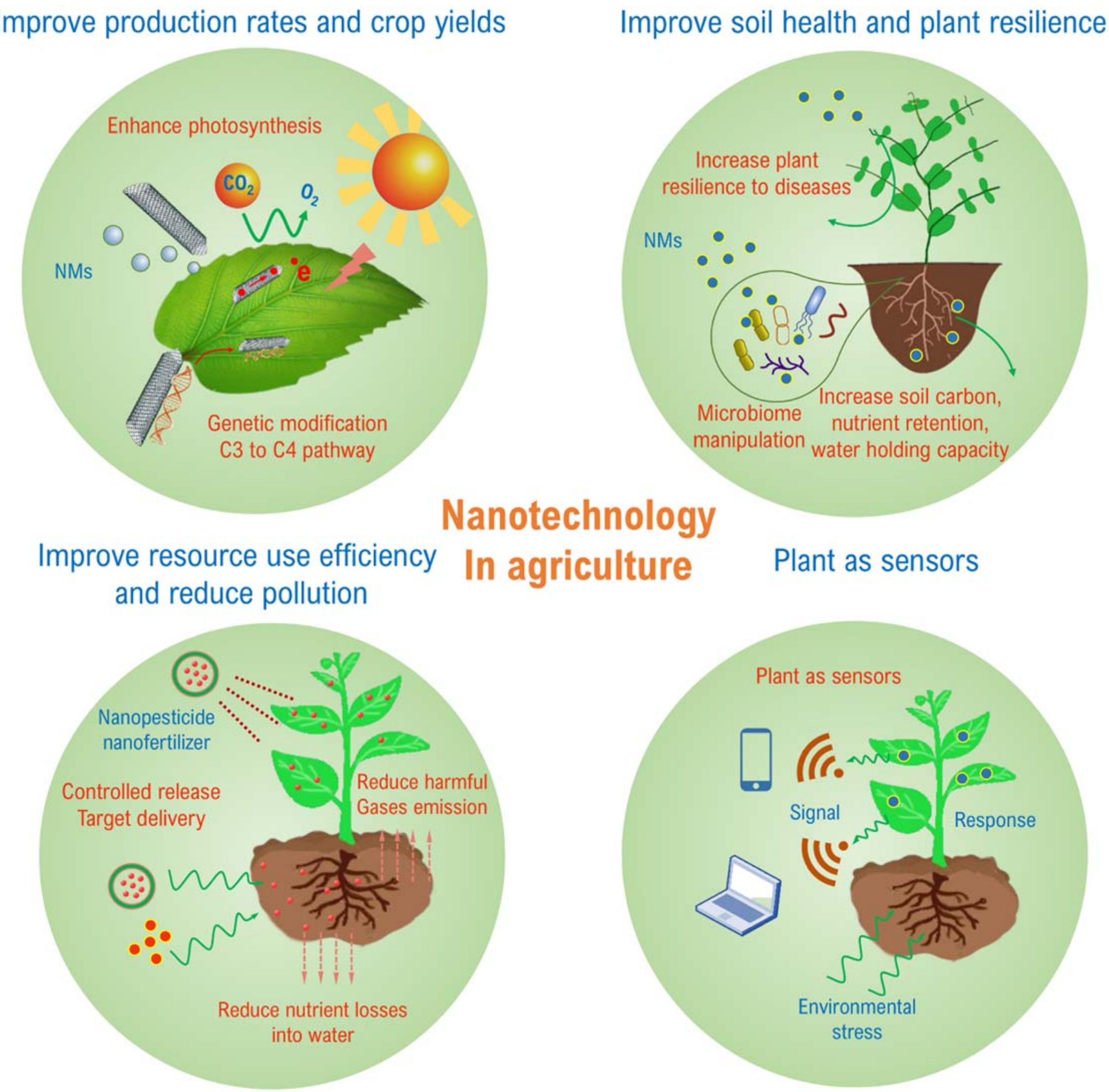

Figure 1. Applications of nanotechnology in agriculture, focusing specifically on crop production (agronomy). Most are still at research stage, due to uncertainties regarding safety, and complex and emerging regulatory processes for approval of agricultural chemicals, including plant protecton products, biocides and fertilizing products or plant biostimulants.

Increasing crop yields and production rates

The Green Revolution relied highly on the traditional agronomic factors including use of synthetic fertilizer and pesticide coupled to rainfall patterns or irrigation, and breeding technology. Instead of increasing intensity and doses of those activities, improving the "efficiency" in agriculture is a more realistic strategy to realise significant enhancement of crop yield and production rates whilst avoiding overuse of natural resources and reducing agricultural pollution, ensuring a win-win-win future. Nanotechnology is undoubtedly one of the most promising approaches that can achieve this goal.

One promising way to enhance crop yield is using 'plant nanobionics', a recently coined term referring to the approach of designing NMs to interact with plants in order to enhance native functions or to give the plant non-native functions[9]. A key focus is to improve the efficiency of photosynthesis, an essential process occurring in plant leaves which uses solar energy to produce sugar from CO_2 and water for plant growth. Photosynthesis efficiency can be enhanced by improving the efficiency of the photosynthetic enzyme ribulose-1,5-bisphos-phate carboxylase/oxygenase (RuBisCO). A pioneering study found that TiO_2 NMs promote the photosynthesis rate by activating the RuBisCO carboxylation process, potentially the result of the photocatalytic activity of TiO_2 NMs[54]. More recently, root application of carbon dots (CDs) was found to enhance RuBisCO activity thus improving the photosynthesis efficiency and carbonhydrate production in *Arabidopsis thaliana*[55], leading to 20% increase of plant yield; this enhancement of plant growth was also demonstrated for several other plant species such as soybean, tomato and eggplant. The overlapping adsorption of CDs with chloroplasts at 420 ~ 700 nm and the photo-induced electron donating and accepting properties of CDs are considered to contribute to the enhanced photosynthesis efficiency. Other NMs, such as multiwalled carbon nanotubes (MWCNTs)[56] and CeO_2 NMs have also shown potential for improving plant phtosynthesis under stress conditions[57, 58]. CeO_2 NMs can scavenge free radicals such as hydroxyls in mesophyll cells thereby improving plant tolerance to stress and photosynthesis.

Enhanced photosynthesis can also be achieved by broadening the range of solar light that can be absorbed by plant leaves. Plants can naturally only absorb visible light in the range 400 ~ 700 nm with energy conversion efficiency less than 4%. Single walled carbon nanotubes (SWCNTs) are capable of capturing a broad range of solar light covering ultraviolet, green and near-infrared. Seminal work by Giraldo et al. found that SWCNTs can insert into the thylakoid membrane, and that the formed assemblies enabled a higher rate of electron transport and augmentation of photosynthesis in leaves due to the semi-conductive nature and wide light absorption ability of SWCNTs[9]. Using SWCNTs as a carrier also enabled gene-delivery into chloroplast, a structure that is hard to target using current (often liposome-based) methods[59], to improve light capture efficiency. The nanotubes also prevented the non-native DNA from integrating into the plant genome thus avoiding consumer concerns over genetically modified crops. Importantly, the delivery efficiency is plant species independent and may help with high-throughput screening of plants to identify phenotypes with desired functions, e.g., optimised photosynthesis efficiency. For example, it could facilitate the engineering of C3 crops (e.g., rice, wheat) to use the C4 pathway (e.g., maize), which have nearly 50% higher light use efficiency and higher N and water use efficiency than C3 pathway plants.

Improving resource use efficiency and soil health

As discussed by Lowry et al.[4], NMs and nanotechnolgy could also improve the use efficiency of natural resources whilst reducing agricultural derived environmental pollution, which is one of the main pillars of the sustainable vision. Crop yield is highly dependent on external inputs of N, P and potassium (K) and micronutrients (e.g., B, Fe, Mn, Cu, Zn) into the agricultural land. The overall NUE by plants currently stands at less than 50% globaly[40], with the rest retained in soil, leached into water, or emited into air, causing detrimental environmental impacts. Engineered NMs offers great opportunity to improve NUE *via* nano-based smart delivery platforms, i.e. so-called controlled release and targeted delivery for efficient plant uptake[60], or through NM influence on microbial communities and their nitrogen fixing abilities[55]. For example, using hydroxyapatite nanoneedles as carriers of urea can remarkably slow the release rate of urea from the nanohybrid surface, which can lead to better yields at

50% lower application rate and reduced hydrolysis of urea and hence lower emission of ammonia into the air.[6] Such a system could also deliver pesticide active ingredients more efficiently thus reducing the amount of pesticides needed. For example, nano copper pesticides show four orders higher efficacy against bacterial blight on pomegranate at 10^4 times lower concentrations than that recommended for copper oxychloride[61]. Nanotechnology also allows the nutrients or pesticides to be delivered only at the target position, such as the plant rhizosphere. These strategies reduce the use of fertilizers and pesticides which would reduce the waste of natural resources and synthetic agrochemicals whilst also protecting soil health by lowering the input of contaminants. In addition to avoiding emissions from agrochemicals, Lowry et al.[4] also pointed out that selective removal or recovery of nutrients from contaminant water and waste streams using nanotechnology provide additional opportunities for improving NUE. NMs applied to soil have been shown to alter the microbiome activity and abundance[62], thus could potentially be used to intentionally alter the singaling and community structure of microbiome (e.g., N fixating bacteria) to enhance the availability of nutrients to plants. It is also possible to increase the population of beneficial symbiotic bacteria (endophyte) to enhance crop productivity; however, as noted by Lowry et al., achieving this requires better understanding of the connection of soil and plant microbiome and the plant physiology involved[63]. One primising approach to address these knowledge gaps, and facilitate development of initial A.I. models, could be soilless growth systems such as hydroponics[64], where introduction plant growth-promoting rhizobacteria and use of multi-element sensors and interpretation algorithms based on machine learning logic to monitor the availability of nutrients/elements in the hydroponic solution and to modify its composition in *realtime*[65], are feasible in the near team and the lessons learned can then be translated to more complex soil systems.

Improving management of soil health and plant growth

Nanotechnology can also enable smart sensing of undesirable ambient biotic (plant pathogens, weed competition, insect damage) and abiotic (drought or flooding, high salanity, extreme climate) stressors, thus improving management effectiveness to reduce crop loss, which is a major challenge in global agronomy. Nanotechnology based approaches for monitoring plant stress and resource deficiencies has been recently reviewed by Giraldo et al[5]. For example, the secretome of microbes, fungi, rhizosphere and plants are rich in information about the organisms adaption to their environment, and offer a means to probe changes in the environment, or stress responses *via* secretion of biomarkers[63, 66]. Developed inventories of secreted proteins under normal, biotic and abiotic stress conditions revealed several different types of novel secreted proteins, such as leaderless secretory proteins potentially involved in the defense/stress responses, which could be explored (including computationally, see later sections for details) for use as biomarkers[63]. Molecule specific NMs-based sensors could be designed to detect metabolites and root exudates to monitor crop growth status. Remote and real time detection of plant pathogens or pests is also possible using NMs sensors, which could greatly reduce the use of pesticides, especially if coupled with stimuli-responsive release[67, 68]. Stimuli responsive sensing systems can deliver agrochemicals only when it is necessary in response to environmental changes such as shortage of nutrients, extreme pH conditions, elevated temperature or CO_2. These strategies will greatly improve agronomic management and resilience of agroecosystems to stress, especially under changing climate conditions.

In order to maximise the use of NMs in agriculture and agronomy, however, there are some concerns that need to be addressed, including the potential toxicity of the NMs to non-target organisms and adverse impacts on ecosystems[69, 70], their persistence and mobility in the environment and that of their break-down or transformation products. As with all agrochemicals, concerns about potential residues in edible portions of plants also need to be addressed, as part of an overall risk assessment of nano-enabled agrochemicals[68]. Since the use of NMs in farmland will require large quantities of NMs, the synthesis of which requires high energy input, evaluating the cost of NMs production and the benefit trade-offs should be considered in the development of NMs for application in agriculture.

While in terms of both risk and application of NMs, current studies in the lab, mesocosms and field are expensive, time-consuming and complicated, limiting the range of conditions that can be varied systematically. Results are often hard to conclude because the interpretation of the results is influenced by factors such as experimental procedures, protocols, duration, NMs types, doses, soil types and plant species. Integrating of the existing data, albeit with gaps and limitations, and supplementation with predictive modelling and machine learning approaches, including Bayesian networks[71, 72], for example, which can be dynamically updated as new knowledge emerges, into IATA offer exciting new directions; development of a nano-agriculture IATA case study utilsiing the OECD IATA case study approach[73] to seems like a logical next step (**Figure 2**).

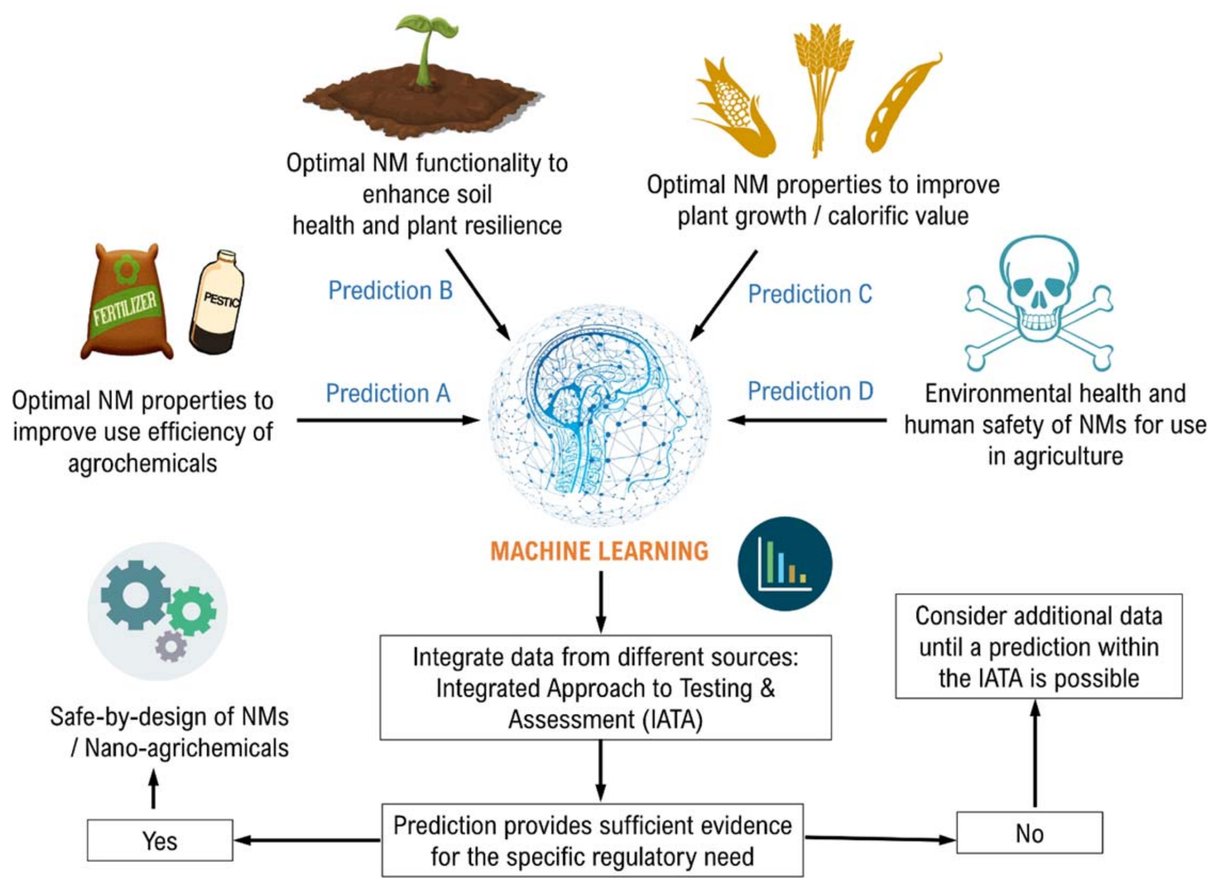

Figure 2. Application of machine learning in risk assessment and safe-by-design of NMs and their extension to support nano-enabled agriculture, building on advances in both nanoinformatics and agricultural systems modelling. Integrating different modelling and experimental approaches, *via* an IATA, will lead to enhanced prediction power and faster and safer implementation of precision nano-enabled agriculture.

A.I. and machine learning for agronomy

A.I. and machine learning approaches

As computer power increases, and the value of data as knowledge to be exploited is realized more and more, A.I. and machine or deep learning approaches are emerging as means to identify patterns in large datasets that are predicitve of future outcomes. One of the most widely used approaches involves neural networks algorithms, which use an unbiased subset of the total available data as the training set to develop a model that makes predictions using the rest of the data and the validity of the predictions are evaluated to ensure that they could not arise randomly. The size and range of the dataset used to train the model provides the limits to its predictive power, or its domain of applicability – models cannot predict reliably outside their range of data. Box 1 describes the various types of data-driven machine learning models, among which are models that link structure or properties (e.g. of a chemical) to specific effects or impacts on the environment, so called Quantitative Structure Activity (or Property) Relationship models (QSARs / QPARs)[74], and Bayesian Networks (BNs) which are a powerful tool for incorporating uncertainty into decision support systems[75], by providing a basis for probabilistic inference and facilitating assessment of changes in probabilistic belief as new evidence is entered into the model. The larger the dataset available to train a machine learning model, the more powerful it will be – typically in drug discovery or chemoinformatics for example, models will utilize data from thousands of different chemicals to develop a prediction. Similarly, genomics and related approaches, where hundreds of thousands of datapoints are available, allow generation of strong gene interaction networks and assessment of effects of specific genetic perturbations, for example used to understand gene regulation networks in plants[76].

Box 1. The main types of Machine Learning algorithms, and examples of their application in agriculture and/or nanomaterials design and safety assessment[77]
• **Supervised Learning.** This algorithm consists of a target outcome (dependent variable) to be predicted from a given set of predictors (independent variables), generating a function that maps inputs to desired outputs. The training process continues until the model achieves the desired level of accuracy on the training dataset, and is then tested on the test dataset that was not involved in the training procedure. *Examples of Supervised Learning*: Regression, Decision Tree, Random Forest, K nearest neighbours (KNN), Logistic Regression *Applications in agriculture and agronomy*: A KNN algorithm was used to predict water retention at -33- and -1500-kPa matric potentials, using a hierarchical set of inputs (soil texture, bulk density, and organic matter content). *Applications in NMs design, safety and interactions*[78]: KNN algorithms have been applied to develop a predictive QSAR model for NMs cellular association based on their physico-chemcial properties and adsorbed protein corona, as a means to understand the drivers of NMs toxicity[79]. *Potential applications in nano-enabled agriculture:* could be applied to prediction of acquired biomolecule coronas (rhiozosphere secretions, foliar sections and biont) and their evolution during NMs uptake into plants; for prediction of NMs trasnformations and impacts on soil or foliar bionts. As part of IATA could be integrated with water retention models to predict NMs mobility in soil. • **Unsupervised Learning.** In this algorithm, there is no target or outcome variable to predict. It is used for clustering data into different groups. *Examples of Unsupervised Learning*: A priori algorithm, K-means. *Applications in agriculture and agronomy*: A segmentation algorithm, inspired from an image-processing region-merging algorithm, for delineation of discrete contiguous management zones has been developed that is applicable to high- or low-density irregular data sets, such as yield data[80], and can identify coherent management units to facilitate differential crop management. *Applications in NMs design, safety and interactions*: K-means clustering has been applied to signal processing of spICP-MS raw data (used for characterisation of NMs size and to distinguish particulate versus ionic fractions for quantification of NMs dissolution, uptake etc.) to discriminate particle signals from background signals, leading to a sophisticated, statistically based method to quantitatively resolve different size groups contained within a NM suspension[81]. *Potential applications in nano-enabled agriculture:* could be applied to predction of NMs transformations under different soil and climate conditions; for prediction and clustering of efficacy of nano-enabled agrichemcials and NUE of fertilisers. Integration with crop management approaches could be applied to determine optimal nano-agrichemical application strategies. • **Reinforcement Learning.** The machine is trained to make specific decisions. Using trial and error, the machine learns from past experience and tries to capture the best possible knowledge to make accurate decisions. *Example of Reinforcement Learning*: Markov Decision Process. *Applications in agriculture and agronomy*: A smart agriculture Internet of Things system based on deep reinforcement learning has been developed to increase food production using deep reinforcement learning in the cloud layer to make immediate smart decisions such as determining the amount of water needed for irrigation to improve the crop growth environment[82]. *Applications in NMs deisgn, safety and interactions*: A recent example used Kohonen networks[83], or self-organising maps (SOMs), to visualise sets of silver and platinum NMs based on structural similarity and overlay functional properties to reveal hidden patterns and structure/property relationships. Visual inspection of the SOMs revealed a strong structure/property relationship between the shape of silver NMs and the energy of their Fermi level, and a weaker relationship between shapes with a high fraction of (111) surface area and the ionisation potential, electron affinity and electronic band gap. Both energy levels and crystal structure or exposed crysal face are linked to NMs reactivity and toxicity[84]. *Potential applications in nano-enabled agriculture:* initial applications in hydroponics as part of realtime responsiveness to changes in nutrient and microbial compositions and integration with NMs structure-property relationships under different environmental and local conditions to optimize release rates and

NUE.

Current A.I. and machine learning in agriculture

A 2018 review of the use of machine learning in agriculture has classified the application areas into (a) crop management, including applications on yield prediction, disease detection, weed detection crop quality, and species recognition; (b) livestock management, including applications on animal welfare and livestock production; (c) water management (daily, weekly, or monthly evapotranspiration rates); and (d) soil management such as prediction-identification of agricultural soil properties[85] . Application of Bayesian Networks to agricultural systems has been a challenge to date however, as there is often insufficient data for computing the prior and conditional probabilities required for the network[75].

In terms of the key areas identified for improvements in crop production, process based machine learning models (e.g., the SPACSYS model[86]) for plant growth, incorporating assimilation, respiration, water and N uptake, partitioning of photosynthate and N, N-fixation for legume plants and root growth[87], are emerging and being constantly improved. With increased understanding of the processes, and the availability of intervention strategies such as precision nanoagrochemicals, the potential of machine learning for optimisaiton of agroecosystems has never been higher; integrating machine learning, simulation, and portfolio optimization can inform decisions and support selection of optimal seed (e.g., soybean) varieties to grow with resolution at the level of a specific farm with its individual crop rotation history rather than at regional scale based on soil type and quality [88]. Indeed, a very recent review of the potential impacts of A.I. on the achievement of the UN sustainable development goals (SDGs) suggested that A.I. will be an enabler for SDG2 on sustainable agriculture, but highlights generally that the pace of development of A.I. may have implications in terms of a lack of regulatory oversight and insight, which could potentially result in gaps in transparency, safety, and ethical standards[89].

Nanoinformatics models applicable to nano-enabled agriculture

The application of machine learning in NM risk assessment, and for design of "safe" and environmentally friendly NMs, is also an area of intensive research in the last few years. For example, nanoQSAR models linking specific NMs properties to uptake by, and impacts on, cells or organisms are emerging, as well as models that allow determination of surface functionalizations that enhance (or decrease), for example, protein binding and/or cellular association (as a pre-requisite for internalization[79]), and can be applied for design of targeting strategies in precision nano-agriculture. Similarly, extending advances in nanomedicine to precision nanoagriculture will facilitate the design of optimized controlled release agrochemicals[90, 91]. For example, deep learning employing an automatic data splitting algorithm and the evaluation criteria suitable for pharmaceutical formulation data was developed for the prediction of optimal pharmaceutical formulations and doses[92]. From an agricultural perspective, understanding the factors (NM, plant, soil, climate etc.) that control the release rate of active ingredients, and the factors driving transport of the carrier can influence selection of formulation parameters. Such data-driven models require significant amounts of data to train and validate them, which is certainly a barrier to their current development, although significant work is underway in the nanosafety arena broadly to develop optimized workflows for data and metadata generation (e.g. utilizing Elecronic Laboratory Notebooks), annotation with relevant ontological terms mapped to the data schema of the receiving databases and automated upload to nanosafety knowledgebases[93], which in the medium term will facilitate the aggregation, integration and re-use of nanosafety and nano-agriculture related datasets.

As noted above however, there are significant concerns regarding the safety and risk of NMs that must be addressed before their widespread intentional application to the environment can be sanctioned, and there are tight regulatory processes for approval of agrochemicals[94]. A recent review has assessed the regulation of pesticides for risk assessment and the potential use of *in silico* computer-based chemical modeling technologies to facilitate risk assessment of nano-enabled pesticides[92]. This review concluded that while quantum chemistry is an appropriate tool to characterize the structure and relative stabilities of organic compounds isomers, for studying degradation processes pathways, and *via* use of quantum descriptors for QSAR development, a reevaluation for their suitability for nano-enabled agriculture is needed.

Challenges and barriers to precision nano-agriculture

Although nanotechnology demonstrates high potential in a wide range of applications in agriculture, it is still primarily at the research stage. There are many challenges to be overcome to move this area forward from basic research to full commercial scale application. This includes lack of mechanistic understanding of the interaction at NM-plant-soil interface and NM uptake and translocation in plant vascular structure and organells; insufficient understanding of the environmental safety and human health risks of intentional NM application; lack of soil and large scale field study to demonstrate the efficacy of NMs under realistic scenarios; and an unclear balance between adoption of a new technology and the low profit margin in agriculture, and the aforementioned challenges regarding collection and harmonization of the datasets needed for development of A.I models.

Long term studies at ecosystem level under environmentally relevant conditions are currently lacking. For example, silver-, zinc- and copper-based NMs show the potential to be applied as efficient pesticides or fungicide; however, the potential impact on non-target organisms (e.g., beneficial plant rhizosphere bacteria, worms) and long term impacts on soil quality are not known. Although nanofertilizers may enhance the NUE, effects (e.g., alteration of the content of carbonhydrates, macro- or micro- nutrient) of NMs on the nutritional quality of food have been reported[95] and need to be assessed systematically and predictive models need to be established. NMs might accumulate in seeds and the potential to cause transgeneration effects[96, 97] are largely unknown. The presence of NMs may cause enhanced uptake of contaminants by plants, e.g. by binding to the NM surface and co-transport, and may amplify their adverse effects[98, 99]. Such co-effects need to be fully understood.

NMs undergo numerous transformations (physically, chemically or biologically) in soils and plants. For example, many metal based NMs such as ZnO, Cu and Ag tend to dissolve and release metal ions, which can further react with soil and plant components such as phosphate, sulfur, chloride *etc*. The original NM properties that are designed for specifc application purpose might not be maintained due to these processes. For example, antifungal NMs such as Ag NMs can be oxidized, dissolve and sufildized in soil environments either by interaction with the soil microbiome or within plants, and the antifungal property of the Ag NMs could be reduced or diminished[100]. Some transformations might release toxic components, for example, graphene oxide was reported to degrade under sunlight and relase PAH (polycyclic aromatic hydrocarbon) -like compounds which are likely to exhibt toxic properties and persist in the environment[101].

Computational tools that can predict NM transformation processes will favour the design to manipulate or even simulate directly the transformation in order to maintain the NM function or modify their impacts. However, the complexity of soil chemistry and the high responsivity of plants and their secretions into the rhizosphere increase the variability and diversty of potential NM transformations (**Figure 3**). Many factors are interlinked. For example, NM transformations are affected by the soil and plant microbiome and the excreted extracellular polymeric substances (EPS) and plant root exudates around the rhizosphere. However, plant root exudate composition and microbiome can affect each other and both may be altered due to NM exposure, which can in-turn affect the NM transformation processes. Changes to the microbiome will affect the N cycling processes in soil. Foliar applied NMs can translocated downwards to root and interact with phyllosphere components such as microorganism and leaf exudates. All of the above are also subject to further change and disruption as a result of climate changes, *e.g.,* altered CO_2 and temperatures can shift nutrient cycling, alter rates of reactions /

trasnformations, change plant susceptibility to NMs and more. Therefore, the dynamic nature of the whole system needs to be considered making this a perfect candidate for A.I. and machine learning solutions.

Compared to small molecules toxicity prediction, nanoinformaticians are used to working with smaller datasets (sometimes just a few NM variants), and use exposure concentrations and timepoints as a means to expand the dataset. Thus, evaluation of the impact of NMs on NUE in a hydrophnic system for example could evaluate a panel of 8-10 NMs and evaluate their effect alone and in combination with fertilizer at different ratios and over different timescales, and determine the N concentrations in the water, plant mass and emitted to air under controlled temperatures and CO_2 levels, which would provide a multi-factorial dataset for establishment of machine learning models to predict the NUE of a new NM, as long as its physicochemical characteristics fell within the domain of applicability of the model, i.e. at least one of the NMs in the training and test set had some overlap with the properties of the "new" NM. If the NMs were characterisered over time under the different conditions, e.g., in terms of their size, dissolution, acquired corona composition, further models predicting corona composition and NMs fate and behaviour could be build, identifying the key NMs properties and environmental factors driving the specific effect. If data on plant growth (roots, shoots) or localization of the NMs in the plants were determined, increasingly complete models of NUE versus localsiation in plants could be developed. System complexity can then be build by moving to soils for example, where the NM characterization challenges increase, but where models for the NMs environmental fate already exist, such as the NanoFASE soil-water-organism model, which predict the fate of NMs in the environment[21]. Thus, the steps will be small initially, but as the datasets and models emerge, their integration with other models and tools into overall IATA and agricultural systems models will become feasible and achievable.

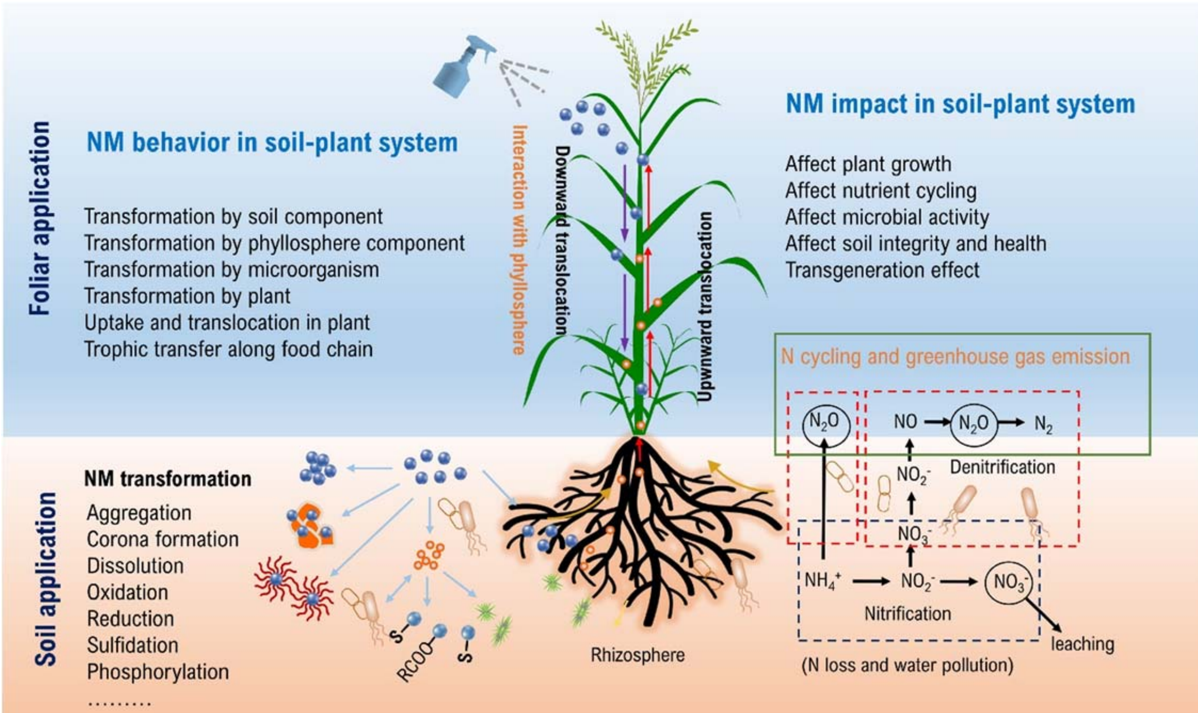

Figure 3. Schematic illustration of the complexity of NM behavior in the soil-plant environment and the potential impacts in soil-plant systems. Understanding and predicting these translocation, transformations, and identifying the optimal NMs forms to retain bioavailable N species in the soil will facilitate design of sustainably functional NMs for agriculture, enhancing NUE while simultaneously reducing pollution and the need for fertlizers. Coupling this with enhanced targeting and sustained, controlled release of pesticides can be facilitated using A.I. to design optimal nano-agrichemicals.

A roadmap for progress

Smart and nano-enabled agriculture, combined with A.I. and machine learning capability offer an exciting convergence of technologies with the unique capability to address the overarching UN SDGs, the "improved nutrition and promotion of sustainable agriculture". The impetus for smart agriculture is thus multi-pronged: from enhancing and sustaining productivity through nano-enabled (responsive) delivery of agrochemicals to crops, through to reduction in environmental pollution and negative human health impacts from agriculture. Agriculture's grand challenges can only be solved if the power of NMs can be harnessed safely, responsibly and sustainably. Nanoinformatics will play a vital role in probing the design parameters, the plant and ecosystem responses, and their co-optimising for safe and sustainable agriculture. For example, A.I. may predict NM impacts on the agricultural ecosystem and their performance in improving agricultural production (NUE, reduction in air and water pollution forms of key elements), by integrating experimental data from across different soil conditions and different plant species/climate change conditions and NM physicochemical properties, which enables safer-by-design development of nanoagricultural chemicals. Future reseach directions are outlined here to address these challenges – a summary of the future research needs is given in Box 2.

Box 2 Future research needs

- Determine the long term fate of NMs including transformation, transport in soil, uptake and translocation in plants, curate this data and its accompanying metadata into NMs-KnowledgeBases and enrich it with global soil and weather characteristics, plant biology knowledge and microbial community characteristics to facilitate development of deep learing models tailored to specific NMs being developed for nano-agriculture and the local environmental conditions.
- Assess the long term life cycle impacts of NMs in agricultural ecosystems including the trophic transfer of NMs along food chains and the potential for transgenerational impacts. Integration of these datasets into the aforementioned KnoweldgeBases will enable further iteration of the models, including development of Integrated Approaches to Testing and Assessment (IATA) and integrated agricultural systems models.
- Take a systems levels approach (as illustrated in **Figure 3**) since the whole ecosystem is interlinked with numerous co-variances, and feed this enhanced understanding into emerging regulatory frameworks.
- Utilise A.I. and machine learning to identify key nanospecific properties that initiate the adverse effects or beneficial function of NMs from large dataset obtained, thereby facilitating design of optimalised (safe-by-design) nano-agrochemicals that are fully compliant with emerging regulations.
- Integrate models addressing different aspects of the overall challenge (physics-based, process based and data driven) through alignment of input and output parameters and development of an IATA, as shown

schematically in **Figure 2**.

1) Understand the long term fate of NMs in agricultural environment including transport, transformation in soil, and uptake and translocation in plant. Transformation of NMs will change their original designed properties, which may defunctionalize their use as fertilizers, pesticides, carriers, or sensors. The transformation could occur in soil, at plant interface (e.g., root or leaf surface) and inside plant. In soil, the transformation could be driven by soil texture and chemistry, and by interaction with soil microorganisms and animals. Plant interfaces, including the rhizosphere and phyllosphere (surface of plant leaves and stems), are critical locations for NMs transformation. The dynamic and complex composition at the these regions, including plant metabolites and microorganisms, drive the transformation. NMs may also transform during their translocation in plant vascular structure by interacting with plant fluids. All these area are largely unknown.

Another critical question is how to effectively deliver NMs to target places in plant. This requires a clear understanding of the uptake and translocation of NM in plants. Both plant leaf and root have physiological barriers to prevent the entry of unwanted substances, while the structure of these two organs are very different. NMs that enter into leaf will translocate downward in phloem, while NMs entering into roots translocate upward in the xylem. The fluid composition and flow rate in xylem and phloem may greatly affect the translocation and accumulation of NMs in plant. Data and predictive models for these questions are all required urgently.

2) Assess the long term life cycle impact of NMs in agricultural ecosystem. Given the fact that repeated application of nanotechnology in agriculture is possible in the future, long term retention of NMs in agriculture soil is inevitable. The majority of the current studies regarding the plant-NMs interaction are phenomenological observations of NMs toxicity under short term, high dose conditions; long term low dose effects of NMs on agroecosystem therefore need to be studied, addressing NM impacts on plant growth, microbial acitivity and community structure, soil health (e.g., soil enzyme activity, nutrient cycling), trophic transfer of NMs and transgeneration effects.

3) Take a systems level approach to nano-enabled agriculture. The behavior, fate and impact of NMs in soil-plant system, and plant and microorganisms are all interconnected. As shown in **Figure 3** and described above, change of one factor may induce a change of the whole system. Given the power of A.I., and the complexity of the optimization challenges facing nano-agriculture, it is clear that their convergence offers exciting new directions (**Figure 4**). Utilising extensive existing models and datasets for soil quality, crop yield and NUE, for example, and combining these with models and datasets related to plant and microbial secretomes, and nanomaterials physicochemical properties, trasnformations and bioavailability, and release of active ingredients, could enable important new insights into (1) the likely transformation pathways for the NMs and their resulting environmental transport and bioavailablity; (2) the potential impact of the NM and their associated active ingredients (in cases where the NMs are carriers) on crop yield and NUE; and (3) potential identification of biomarkers of crop health / diseasae that can be utilized as early warning systems. Identification of data gaps can also drive the design of focused experiments to gap-fill or to develop sub-models to integrate into an overall model framework allowing design of NMs and active ingredient combinations that optimize NUE and minimize pollution whilst enhancing crop yield and potentially even nutritional (calorific) value. Integration of safe-by-design approaches, and feeding forward the emerging knowledge into updating of regulatory process for advanced nano-enabled agricultural applications, both in fertilization and in plant protection is essential also.

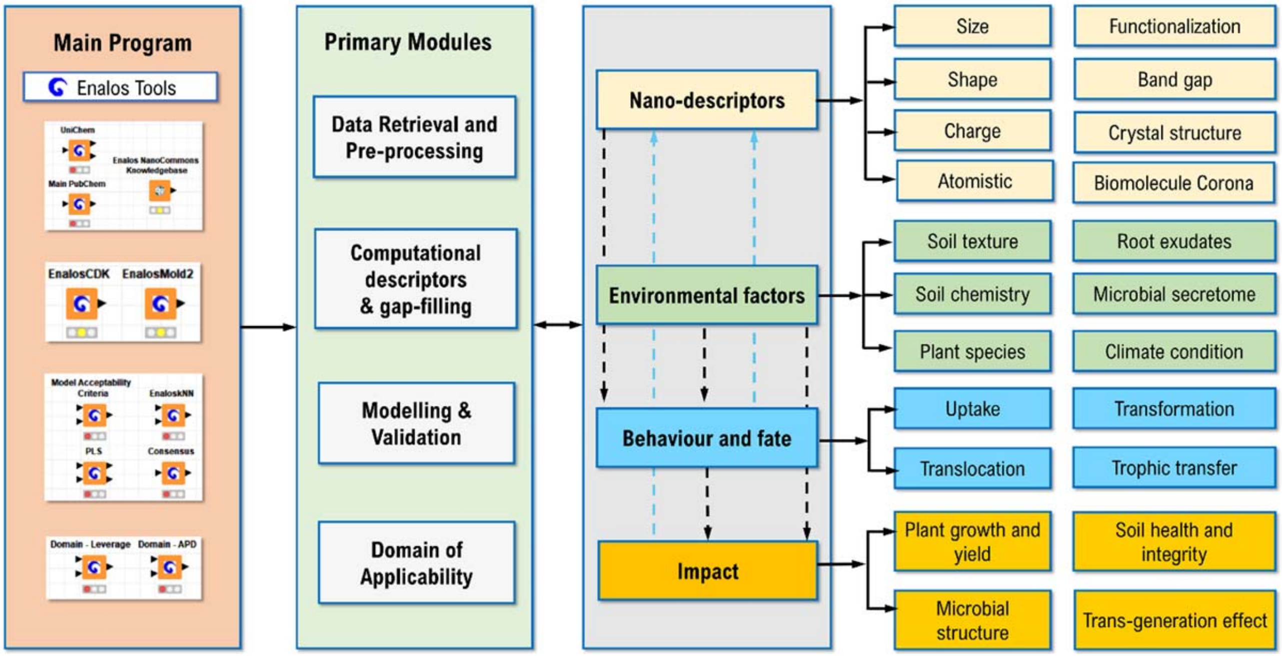

Figure 4. Approach to integration of A.I. models needed to assess ENMs behavior, fate and impact in agriculture based on the interplay between ENM and environmental factors including the crop type and soil characteristics. Integration of automated tools for harvesting data from public databases, preprocessing and curation of the data for direct input into the AI/ML models, for example via the Enalos Tools[102] in KNIME, ensures that the output data from one model can serve as the input data for subsequent models, thereby facilitating model integration and development of increasingly multiplexed predictions for nano-enabled precision agriculture.

4) Utilise A.I. and machine learning to identify key nanospecific properties that initiate the adverse effects or beneficial function of NMs from large datasets obtained through use of automated data retrieval from public databases, data pre-processing and gap-fillling, and data splitting into tets and validateion sets for modelling[102] (Figure 4). There are multiple physicochemical properties of NMs such as size, shape, surface charge, surface area, surface reactivity and crystal structure that can influence their transformations and toxicity. A.I. and machine learning will enable the selection of the most critical parameters that determine the behavior and and the prediction of the behavior of NMs in

soil and plant systems and facilitate the design of NMs that can be delivered to plants efficiently. NM transformation in different soil conditions and different root rhizosphere compositions under changing climate conditions, could be also predicted by integrating predictive models which allowing optimization of NMs for agricultural application in a range of climatic and local conditions. Wider ecosystems effects, and prediction of tripartite (NMs-soil-plant) behaviours under future climate scenarios can also be predicted, utilizing for example Baysian networks. Such models are especially important as they can operate under data scarcity, yet can easily incorporate new data as it emerges. Application of such models to address the broader issues of food security, and to tacking thhe sustainable development goal of "improved nutrition and promote sustainable agriculture" (SDG2) will provide important new intersectional insights and suggestions for ways forward.

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Author contributions

P.Z. and I.L. framed the manuscript. P.Z., Z.G., S.U. and I.L. wrote the masnucript with contributions and inputs from all authors. P.Z., A.A. and G.M. produced the graphics.

Conflict of interests

There are no conflicts of interest to declare.

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Nanotechnology and Artificial Intelligence to Enable Sustainable and Precision Agriculture

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Abstract

Climate change, increasing populations, competing demands on land for production of biofuels, and declining soil quality are challenging global food security. Finding sustainable solutions requires bold new approaches and integration of knowledge from diverse fields, such as materials science and informatics. The convergence of precision agriculture, whereby farmers respond in real-time to changes in crop growth, with nanotechnology and artificial intelligence offers exciting opportunities for sustainable food production. Coupling existing models for nutrient cycling and crop productivity with nanoinformatics approaches to optimize targeting, uptake, delivery nutrient capture and long term impacts on soil microbial communities will allow design of nanoscale agrochemcials that combine optimal safety and functionality profiles.

Introduction

The Green Revolution, i.e. the 3rd Agricultural Revolution, which occurred between the 1950s and 1960s, dramatically increased global agriculture productions yield thereby avoiding the spread of famine and malnutrition. However, the world population has also grown by more than 5 billion since the beginning of the Green Revolution, entailing a continuous growth of crop production. The global agriculture and food security sector is facing a wide spectrum of challenges such as low crop yields, declining soil health and fertility, low use efficiency of agrochemicals due mainly to excessive use of fertilizes and pesticides, shrinking arable land *per capita* and diminishing freshwater availability for irrigation[1]. Moreover, climate change, as arising from increasing atmospheric CO_2 concentration leading to rising temperature, is likely to further affect the resilience of agricultural soils and their ability to sustain productivity and ensure food security for an increasing human population[2]. Nanotechnology offers great potential to enable precision and sustainable agriculture, the opportunities and challenges of which have been discussed in several recent reviews covering strategies to enhance crop nutrition and smart plant sensors[3, 4, 5]. Using nanotechnology, the delivery of fertilizer[6] can be tailored by targeting to specific tissues / organisms and stimuli-responsive release, as well as potentially improving nutrient use efficiency (NUE) by releasing the nutrient slowly for plant uptake[7]. Nano-enabled agriculture is expected to target pests more efficiently using lower amounts of pesticide[8] thereby avoiding widespread impacts on soil health and biodiversity, and improving soil function and nutrient cycling *via* soil microbiome enhancement (optimization of nitriying/denitrifying bacterial communities). Longer term applications include development of smart "sensor" plants, whereby the plant itself is adapted, using targeted delivery of nanomaterials (NMs), for sensing abiotic stress[9]. As with all new technologies however, the risks must be evaluated in parallel with the benefits, and indeed several NMs have been identified to cause negative changes in soil community structure, e.g, TiO_2 NMs cascading negative effects on denitrification enzyme activity and a deep modification of the bacterial community structure after just 90 days of exposure to a realistic concentration of NPs (1 mg kg^{-1} dry soil)[10], while studies with Ag NMs, which are well-known for their antimicrobial activity have shown that the extent of impact on soil community composition over 90 days are affected by exposure time and physicochemical composition of soil as well as the type and coating of the NMs[11]. Thus, an important caveat at the outset of this review is that NMs represent a very broad spectrum of chemistries, compositions and physicochemical properties, which are dynamic and evolving as the NMs interact with their surroundings, and as such generalisations regarding their applications in agriculture are difficult, and predictions of long-term effects are challenging currently.

However, as noted in the aforementioned reviews[3, 4, 5], the development of nanotechnology for agricultural applications is still at an early stage and is moving forward quite slowly. Significant differences may exist between nanotechnology-based pesticides and conventional pesticides, including altered bioavailability, sensitivity, dosimetry, and pharmacokinetics[12, 13]. Challenges and barriers include limited understanding of plant-NMs interactions, limited methods for efficient delivery of NMs to plants and soil, risks of potentially hazardous effects of NMs to human health from accumulation of NMs and active ingredient residues in edible portions of plants[4], and to long term soil quality and soil health from accumulation of NMs and their degradation products in soil and resultant potential alterations in microbial biodiversity[14]. There is an urgent need to address these barriers and achieve a true win-win scenario, whereby improved agricultural production, reduced environmental pollution from agriculture and lower costs for farmers can be achieved synergistically. A one-health approach to nano-agriculture was proposed by Lombi et al., that requires interdisciplinarity and the bridging of human and environmental health research[15]. Computational approaches including artificial intelligence (A.I.) and machine learning (M.L.) modelling will undoubtedly play critical roles in the progess of nano-enabled agriculture, and are already starting to gain regulatory acceptance for NMs safety assessment.

The application of computers and artificial intelligence (A.I.) in agriculture is not new – for example, articles addressing software for integrated resource management[16], image digitization for soil and crop science[16], and light and temperature monitoring and control for plants[17] were published 35 years ago! The rise of remote sensing and integration of remote sensing data into decision support tools for contemporary farming systems is expected to improve yield production and management while reducing operating costs and environmental impact[18]. Agricultural systems models have emerged over the last 50 years, spanning field, farm, landscape, regional, and global spatial scales and engaging questions in past, current, and future time periods. Integrated agricultural systems models combining grasslands and cropping models, livestock models, pest and disease models and risk behaviour models are also emerging, although data gaps exist across all aspects, hampering their implementation[19]. However, the comvergence of A.I. approaches and nano-enabled agriculture is in its infancy and as such the current perspective aims to stimulate the development of this important area.

The rapid pace of the development of nanotechnologies, the enormous diversity of physico-chemical properties of NMs and their dynamic interactions with, and transformations, by their surrroundings (e.g., corona formation, dissolution, sulfidation etc.[20, 21]) leads to the need for *in silico* approaches to predict and assess their safety[22]. Nanoinformatics is a powerful way of relating the nanostrucutural features with functional properties based on data-driven A.I. and M.L. approaches[22, 23, 24]. Nanoinformatics emerged a decade ago in the context that development and implementation of nanotechnology in the real world requires the harnessing of information at the nexus of environmental and human safety, risk assessment and management, physiochemical properties and function. With A.I. and M.L. enabled *in silico* risk assessment[25], NMs grouping and classification[26], and safe-by-design[27] NMs design, as well as for predictions of NMs corona formation[28] and consequences for cellular attachment and uptake[29, 30, 31], nanoinformatics has played significnt roles in the area of nanosafety and nanomedicine, while there is also ample scope of nanoinformatics in nano-enabled agriculture that has not been explored, including for prediction of NMs interactions with and impacts on rhizosphere secretions, NMs transformations before and during uptake and translocation, NMs impacts on soil microbial communities and for predictions up plant uptake following foliar application. Experimetnal data are emerging in all these areas[32, 33, 34], and a dedicated effort to integrate and curate this data, and present it in a format suitable for modelling is currently underway by the authors in the scope of their nanoinformatics e-infrastructure projects NanoCommons and NanoSolveIT[35]. Coupling these approaches with existing models for nutrient cycling[36], NUE[37] and crop productivity[38] and the aforementioned agricultural systems models into an overall Integrated Approach for Testing and Assessment (IATA) will allow co-optimisation of NMs for use in agricultural systems that combine safety and functionality profiles enabling precision agriculture.

In this perspective, emerging applications of nanotechnology and nanoinformatics in agriculture and gaps in current understanding are outlined. Key research areas are identified where the application of A.I. will support the effective implementation of nanotechnology in agriculture, with a view to enhancing productivity and protecting or improving environmental quality. Current applications of A.I. in agriculture, in nanotechnology broadly, and in nano-enabled agriculture are also outlined, along with identification of key areas where their convergence and integration can accelerate the development of sustainable nano-enabled precision agriculture.

Current challenges in agriculture

With an ever increasing human population under a decreasing per capita agricultural land globally[39], a key challenge is to optimize productivity whilst ensuring the conservation of soil health and the protection of environmental quality. Agrochemicals (fertilizers and pesticides) enabled an increase in productivity such that half of us are alive today due to the invention of industrial ammonia production and its use as a fertilizer globally. However, the intensification of agriculture for enhanced productivity resulted in extremely poor NUE globally (<50%)[40, 41]. Poor NUE under an excessive fertilizer use culture thus poses a serious threat to environmental quality as large amounts of nutrients are lost into water and air causing eutrophication and greenhouse effects. For example, agriculture contributes nearly 11% of global greenhouse gas emissions[42]. Nitrogen (N) and phosphorus (P) fertilizer use in agriculture is one of the main drivers behind the breach of the safe planetary boundaries for these elements that could trigger irreparable damage to the environment[43]. Rockstrom et al. recommended a reduction of reactive N use in agriculture from 150 Mt N y^{-1} to about 35 Mt N y^{-1} globally to ensure sustainability[43]. Such a reduction can only be achieved through a combination of approaches including targeted nano-enabled delivery of fertilizer to match plant demands to avoid excessive losses, development and availability of low-cost in situ nutrient sensing technology to help farmers plan fertilization efficiently, introduce rotations into agriculture to recover the health and fertility of soils, utilize farm yard manure and slurries for meeting nutrient demands and identifying crop breed that are efficient in nutrient uptake and even fixing atmospheric N_2 directly or thorugh enhance symbiosis are some of the key measures to enhance NUE, reduce excessive fertilization and the subsequent losses of reactive N from cultivated soil[44]. Unlike N, available terrestrial P reserves are non-renewable and the current losses of available P from agriculture to water (rivers and oceans) is 10 times the pre-industrial and agricultural intensification era[43]. This unsustainable use of P fertilizer in agriculture is thus posing a risk to global food security[45], while causing eutrophication of fresh and coastal water bodies, together with N[41].

The grand challenge in agriculture is therefore that of optimizing usage efficiences, timing and targeting of fertilizer use to enhance and sustain crop production and while simultaneously reducing amounts of fertilizers used and losses to environments external to agricultural catchments. While regulatory and voluntary fertilizer use policies in Europe and USA have resulted in reduction of losses to water, an overall enhancement in NUE was not achieved[46]. Recent efforts to enhance NUE include utilization of biofertilization to enhance microbial biodiversity[47], and application of a range of N management tools across the growing season including soil testing, plant tissue testing, spectral response, fertilizer placement and timing and vegetative indexes (leaf area index, and Normalized Difference Vegetation Index (NDVI)) through A.I. enabled drones, handheld sensors, and satellite imagery[48]. Rockstrom et al. suggested that substantial N and P fertilizer use reduction can protect the planet from breaching resilence thresholds, if such reductions can still ensure productivity[43].

Gobal agricultural yields are also impacted by crop loss due to competition from weeds, insect damage and plant diseases. Weed competition causes 34% of crop loss on a global scale, while microbial diseases and pest damage also cause 34% of crop loss [49]. The application of synthetic herbicides and pesticides thus increases yields (reduces crop loss) and, in the case of herbicides containing N, P and K, improves food quality through enhanced nutrient uptake and retention[50]; however, these agrochemicals, which are designed to kill, also cause severe adverse impacts on the health of human and non-targeted organisms and soil fertility, and result in contamination of water, soil and air[51]. Mis-use of agrichemicals on poor quality soils, soil degradation as a result of farming intensification, shrinking water availability and decreasing water quality, and globalization of diseases have led to low resilience of agriculture systems.[52] Moreover, climate changes such as elevated atmospheric CO_2 levels and increasing temperatures also potentially impact the future of agriculture.[53]

Nanotechnology applications in the agricultural sector have great potential to improve all aspects of crop production, that is, to increase crop production yields and resource use efficiency whilst reducing agriculture-related environmental pollution, thereby ensuring global food security whilst ensuring future agricultural sustainability. Coupling existing models for nutrient cycling and crop productivity with A.I. and machine learning to optimize targeting, uptake, delivery, nutrient capture and soil microbial composition will allow design of nanoscale agrochemcials that combine optimal safety and functionality profiles and implementation of nano-agrichemicals into mainstream agricultural systems management.

Current applications of nanotechnology in agriculture

Nanotechnology offers the benefit of reducing costs of fertilization at farm level directly and at global level, indirectly, through reduction in environmental damage and environmental clean up costs associated with agriculture-derived pollution. More importantly, enhancing NUE through nanotechnology application in agriculture is a promising intervention technology that could revolutionize and modernize agriculture making it precise and targeted. **Figure 1** summarises 4 key areas where nanotechnology is, and will continue to, improve the precision and sustainability of agriculture.

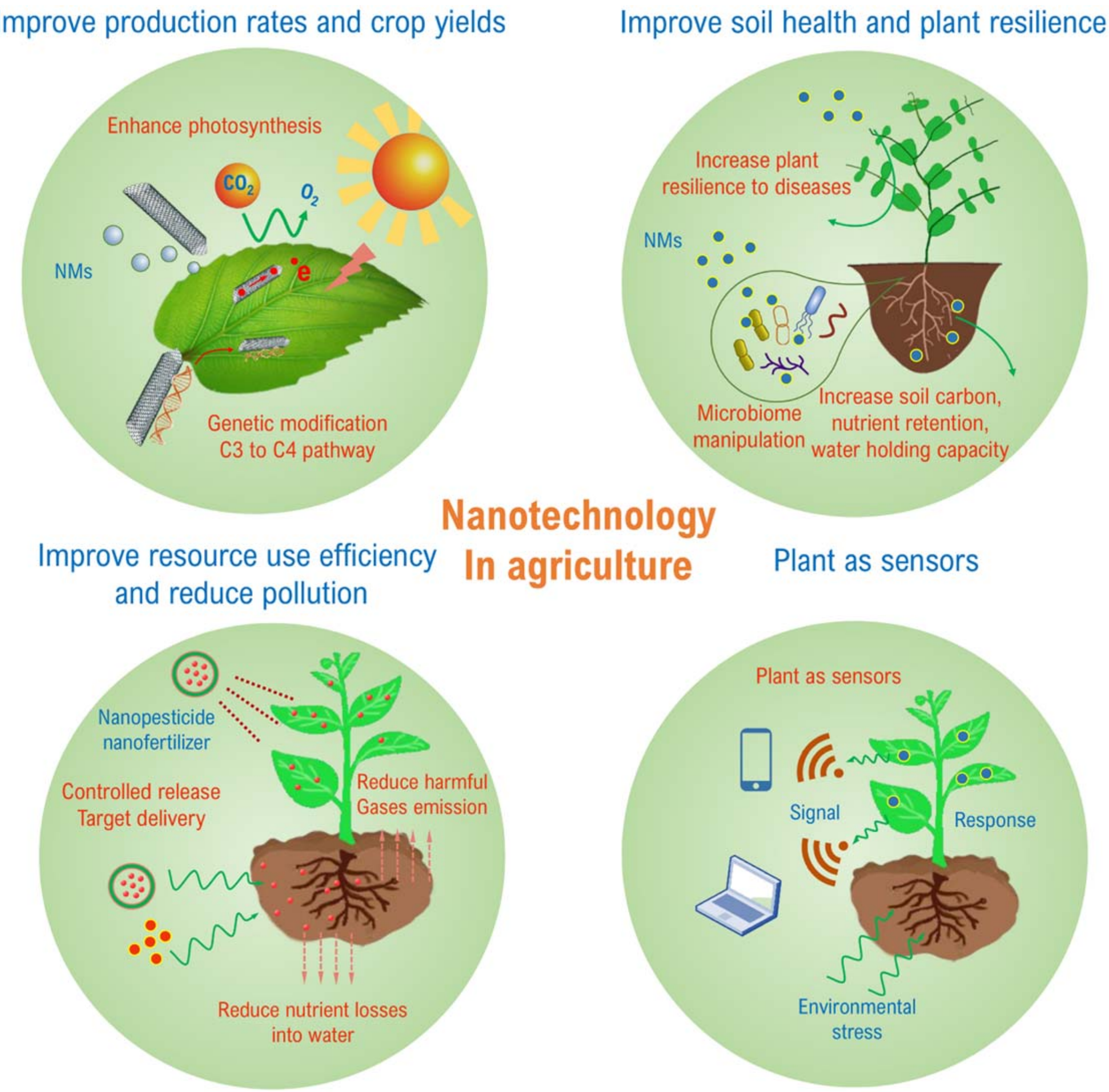

Figure 1. Applications of nanotechnology in agriculture, focusing specifically on crop production (agronomy). Most are still at research stage, due to uncertainties regarding safety, and complex and emerging regulatory processes for approval of agricultural chemicals, including plant protecton products, biocides and fertilizing products or plant biostimulants.

Increasing crop yields and production rates

The Green Revolution relied highly on the traditional agronomic factors including use of synthetic fertilizer and pesticide coupled to rainfall patterns or irrigation, and breeding technology. Instead of increasing intensity and doses of those activities, improving the "efficiency" in agriculture is a more realistic strategy to realise significant enhancement of crop yield and production rates whilst avoiding overuse of natural resources and reducing agricultural pollution, ensuring a win-win-win future. Nanotechnology is undoubtedly one of the most promising approaches that can achieve this goal.

One promising way to enhance crop yield is using 'plant nanobionics', a recently coined term referring to the approach of designing NMs to interact with plants in order to enhance native functions or to give the plant non-native functions[9]. A key focus is to improve the efficiency of photosynthesis, an essential process occurring in plant leaves which uses solar energy to produce sugar from CO_2 and water for plant growth. Photosynthesis efficiency can be enhanced by improving the efficiency of the photosynthetic enzyme ribulose-1,5-bisphos-phate carboxylase/oxygenase (RuBisCO). A pioneering study found that TiO_2 NMs promote the photosynthesis rate by activating the RuBisCO carboxylation process, potentially the result of the photocatalytic activity of TiO_2 NMs[54]. More recently, root application of carbon dots (CDs) was found to enhance RuBisCO activity thus improving the photosynthesis efficiency and carbonhydrate production in *Arabidopsis thaliana*[55], leading to 20% increase of plant yield; this enhancement of plant growth was also demonstrated for several other plant species such as soybean, tomato and eggplant. The overlapping adsorption of CDs with chloroplasts at 420 ~ 700 nm and the photo-induced electron donating and accepting properties of CDs are considered to contribute to the enhanced photosynthesis efficiency. Other NMs, such as multiwalled carbon nanotubes (MWCNTs)[56] and CeO_2 NMs have also shown potential for improving plant phtosynthesis under stress conditions[57, 58]. CeO_2 NMs can scavenge free radicals such as hydroxyls in mesophyll cells thereby improving plant tolerance to stress and photosynthesis.

Enhanced photosynthesis can also be achieved by broadening the range of solar light that can be absorbed by plant leaves. Plants can naturally only absorb visible light in the range 400 ~ 700 nm with energy conversion efficiency less than 4%. Single walled carbon nanotubes (SWCNTs) are capable of capturing a broad range of solar light covering ultraviolet, green and near-infrared. Seminal work by Giraldo et al. found that SWCNTs can insert into the thylakoid membrane, and that the formed assemblies enabled a higher rate of electron transport and augmentation of photosynthesis in leaves due to the semi-conductive nature and wide light absorption ability of SWCNTs[9]. Using SWCNTs as a carrier also enabled gene-delivery into chloroplast, a structure that is hard to target using current (often liposome-based) methods[59], to improve light capture efficiency. The nanotubes also prevented the non-native DNA from integrating into the plant genome thus avoiding consumer concerns over genetically modified crops. Importantly, the delivery efficiency is plant species independent and may help with high-throughput screening of plants to identify phenotypes with desired functions, e.g., optimised photosynthesis efficiency. For example, it could facilitate the engineering of C3 crops (e.g., rice, wheat) to use the C4 pathway (e.g., maize), which have nearly 50% higher light use efficiency and higher N and water use efficiency than C3 pathway plants.

Improving resource use efficiency and soil health

As discussed by Lowry et al.[4], NMs and nanotechnolgy could also improve the use efficiency of natural resources whilst reducing agricultural derived environmental pollution, which is one of the main pillars of the sustainable vision. Crop yield is highly dependent on external inputs of N, P and potassium (K) and micronutrients (e.g., B, Fe, Mn, Cu, Zn) into the agricultural land. The overall NUE by plants currently stands at less than 50% globaly[40], with the rest retained in soil, leached into water, or emited into air, causing detrimental environmental impacts. Engineered NMs offers great opportunity to improve NUE *via* nano-based smart delivery platforms, i.e. so-called controlled release and targeted delivery for efficient plant uptake[60], or through NM influence on microbial communities and their nitrogen fixing abilities[55]. For example, using hydroxyapatite nanoneedles as carriers of urea can remarkably slow the release rate of urea from the nanohybrid surface, which can lead to better yields at

50% lower application rate and reduced hydrolysis of urea and hence lower emission of ammonia into the air.[6] Such a system could also deliver pesticide active ingredients more efficiently thus reducing the amount of pesticides needed. For example, nano copper pesticides show four orders higher efficacy against bacterial blight on pomegranate at 10^4 times lower concentrations than that recommended for copper oxychloride[61]. Nanotechnology also allows the nutrients or pesticides to be delivered only at the target position, such as the plant rhizosphere. These strategies reduce the use of fertilizers and pesticides which would reduce the waste of natural resources and synthetic agrochemicals whilst also protecting soil health by lowering the input of contaminants. In addition to avoiding emissions from agrochemicals, Lowry et al.[4] also pointed out that selective removal or recovery of nutrients from contaminant water and waste streams using nanotechnology provide additional opportunities for improving NUE. NMs applied to soil have been shown to alter the microbiome activity and abundance[62], thus could potentially be used to intentionally alter the singaling and community structure of microbiome (e.g., N fixating bacteria) to enhance the availability of nutrients to plants. It is also possible to increase the population of beneficial symbiotic bacteria (endophyte) to enhance crop productivity; however, as noted by Lowry et al., achieving this requires better understanding of the connection of soil and plant microbiome and the plant physiology involved[63]. One primising approach to address these knowledge gaps, and facilitate development of initial A.I. models, could be soilless growth systems such as hydroponics[64], where introduction plant growth-promoting rhizobacteria and use of multi-element sensors and interpretation algorithms based on machine learning logic to monitor the availability of nutrients/elements in the hydroponic solution and to modify its composition in *realtime*[65], are feasible in the near team and the lessons learned can then be translated to more complex soil systems.

Improving management of soil health and plant growth

Nanotechnology can also enable smart sensing of undesirable ambient biotic (plant pathogens, weed competition, insect damage) and abiotic (drought or flooding, high salanity, extreme climate) stressors, thus improving management effectiveness to reduce crop loss, which is a major challenge in global agronomy. Nanotechnology based approaches for monitoring plant stress and resource deficiencies has been recently reviewed by Giraldo et al[5]. For example, the secretome of microbes, fungi, rhizosphere and plants are rich in information about the organisms adaption to their environment, and offer a means to probe changes in the environment, or stress responses *via* secretion of biomarkers[63, 66]. Developed inventories of secreted proteins under normal, biotic and abiotic stress conditions revealed several different types of novel secreted proteins, such as leaderless secretory proteins potentially involved in the defense/stress responses, which could be explored (including computationally, see later sections for details) for use as biomarkers[63]. Molecule specific NMs-based sensors could be designed to detect metabolites and root exudates to monitor crop growth status. Remote and real time detection of plant pathogens or pests is also possible using NMs sensors, which could greatly reduce the use of pesticides, especially if coupled with stimuli-responsive release[67, 68]. Stimuli responsive sensing systems can deliver agrochemicals only when it is necessary in response to environmental changes such as shortage of nutrients, extreme pH conditions, elevated temperature or CO_2. These strategies will greatly improve agronomic management and resilience of agroecosystems to stress, especially under changing climate conditions.

In order to maximise the use of NMs in agriculture and agronomy, however, there are some concerns that need to be addressed, including the potential toxicity of the NMs to non-target organisms and adverse impacts on ecosystems[69, 70], their persistence and mobility in the environment and that of their break-down or transformation products. As with all agrochemicals, concerns about potential residues in edible portions of plants also need to be addressed, as part of an overall risk assessment of nano-enabled agrochemicals[68]. Since the use of NMs in farmland will require large quantities of NMs, the synthesis of which requires high energy input, evaluating the cost of NMs production and the benefit trade-offs should be considered in the development of NMs for application in agriculture.

While in terms of both risk and application of NMs, current studies in the lab, mesocosms and field are expensive, time-consuming and complicated, limiting the range of conditions that can be varied systematically. Results are often hard to conclude because the interpretation of the results is influenced by factors such as experimental procedures, protocols, duration, NMs types, doses, soil types and plant species. Integrating of the existing data, albeit with gaps and limitations, and supplementation with predictive modelling and machine learning approaches, including Bayesian networks[71, 72], for example, which can be dynamically updated as new knowledge emerges, into IATA offer exciting new directions; development of a nano-agriculture IATA case study utilsiing the OECD IATA case study approach[73] to seems like a logical next step (**Figure 2**).

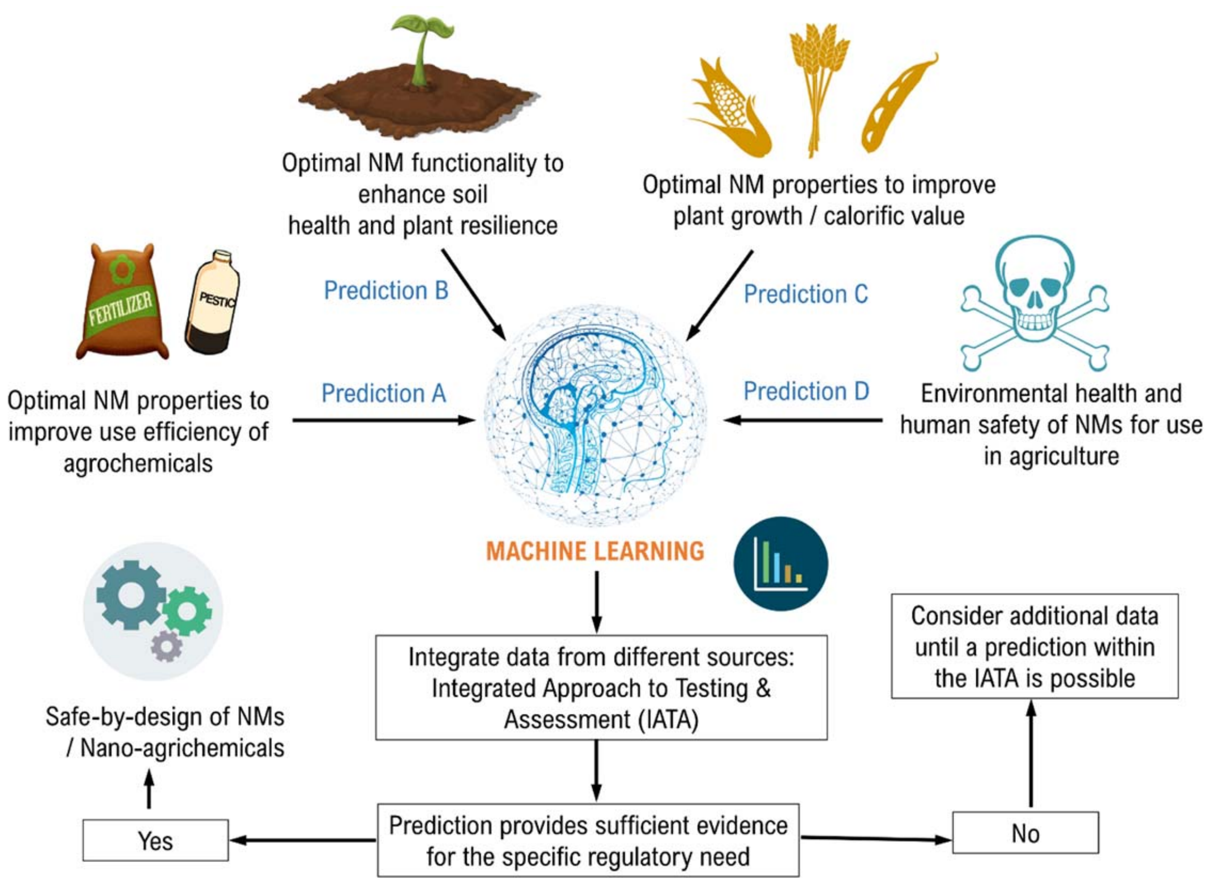

Figure 2. Application of machine learning in risk assessment and safe-by-design of NMs and their extension to support nano-enabled agriculture, building on advances in both nanoinformatics and agricultural systems modelling. Integrating different modelling and experimental approaches, *via* an IATA, will lead to enhanced prediction power and faster and safer implementation of precision nano-enabled agriculture.

A.I. and machine learning for agronomy

A.I. and machine learning approaches

As computer power increases, and the value of data as knowledge to be exploited is realized more and more, A.I. and machine or deep learning approaches are emerging as means to identify patterns in large datasets that are predicitve of future outcomes. One of the most widely used approaches involves neural networks algorithms, which use an unbiased subset of the total available data as the training set to develop a model that makes predictions using the rest of the data and the validity of the predictions are evaluated to ensure that they could not arise randomly. The size and range of the dataset used to train the model provides the limits to its predictive power, or its domain of applicability – models cannot predict reliably outside their range of data. Box 1 describes the various types of data-driven machine learning models, among which are models that link structure or properties (e.g. of a chemical) to specific effects or impacts on the environment, so called Quantitative Structure Activity (or Property) Relationship models (QSARs / QPARs)[74], and Bayesian Networks (BNs) which are a powerful tool for incorporating uncertainty into decision support systems[75], by providing a basis for probabilistic inference and facilitating assessment of changes in probabilistic belief as new evidence is entered into the model. The larger the dataset available to train a machine learning model, the more powerful it will be – typically in drug discovery or chemoinformatics for example, models will utilize data from thousands of different chemicals to develop a prediction. Similarly, genomics and related approaches, where hundreds of thousands of datapoints are available, allow generation of strong gene interaction networks and assessment of effects of specific genetic perturbations, for example used to understand gene regulation networks in plants[76].

Box 1. The main types of Machine Learning algorithms, and examples of their application in agriculture and/or nanomaterials design and safety assessment[77]
• **Supervised Learning.** This algorithm consists of a target outcome (dependent variable) to be predicted from a given set of predictors (independent variables), generating a function that maps inputs to desired outputs. The training process continues until the model achieves the desired level of accuracy on the training dataset, and is then tested on the test dataset that was not involved in the training procedure. *Examples of Supervised Learning*: Regression, Decision Tree, Random Forest, K nearest neighbours (KNN), Logistic Regression *Applications in agriculture and agronomy*: A KNN algorithm was used to predict water retention at -33- and -1500-kPa matric potentials, using a hierarchical set of inputs (soil texture, bulk density, and organic matter content). *Applications in NMs design, safety and interactions*[78]: KNN algorithms have been applied to develop a predictive QSAR model for NMs cellular association based on their physico-chemcial properties and adsorbed protein corona, as a means to understand the drivers of NMs toxicity[79]. *Potential applications in nano-enabled agriculture:* could be applied to prediction of acquired biomolecule coronas (rhiozosphere secretions, foliar sections and biont) and their evolution during NMs uptake into plants; for prediction of NMs trasnformations and impacts on soil or foliar bionts. As part of IATA could be integrated with water retention models to predict NMs mobility in soil. • **Unsupervised Learning.** In this algorithm, there is no target or outcome variable to predict. It is used for clustering data into different groups. *Examples of Unsupervised Learning*: A priori algorithm, K-means. *Applications in agriculture and agronomy*: A segmentation algorithm, inspired from an image-processing region-merging algorithm, for delineation of discrete contiguous management zones has been developed that is applicable to high- or low-density irregular data sets, such as yield data[80], and can identify coherent management units to facilitate differential crop management. *Applications in NMs design, safety and interactions*: K-means clustering has been applied to signal processing of spICP-MS raw data (used for characterisation of NMs size and to distinguish particulate versus ionic fractions for quantification of NMs dissolution, uptake etc.) to discriminate particle signals from background signals, leading to a sophisticated, statistically based method to quantitatively resolve different size groups contained within a NM suspension[81]. *Potential applications in nano-enabled agriculture:* could be applied to predction of NMs transformations under different soil and climate conditions; for prediction and clustering of efficacy of nano-enabled agrichemcials and NUE of fertilisers. Integration with crop management approaches could be applied to determine optimal nano-agrichemical application strategies. • **Reinforcement Learning.** The machine is trained to make specific decisions. Using trial and error, the machine learns from past experience and tries to capture the best possible knowledge to make accurate decisions. *Example of Reinforcement Learning*: Markov Decision Process. *Applications in agriculture and agronomy*: A smart agriculture Internet of Things system based on deep reinforcement learning has been developed to increase food production using deep reinforcement learning in the cloud layer to make immediate smart decisions such as determining the amount of water needed for irrigation to improve the crop growth environment[82]. *Applications in NMs deisgn, safety and interactions*: A recent example used Kohonen networks[83], or self-organising maps (SOMs), to visualise sets of silver and platinum NMs based on structural similarity and overlay functional properties to reveal hidden patterns and structure/property relationships. Visual inspection of the SOMs revealed a strong structure/property relationship between the shape of silver NMs and the energy of their Fermi level, and a weaker relationship between shapes with a high fraction of (111) surface area and the ionisation potential, electron affinity and electronic band gap. Both energy levels and crystal structure or exposed crysal face are linked to NMs reactivity and toxicity[84]. *Potential applications in nano-enabled agriculture:* initial applications in hydroponics as part of realtime responsiveness to changes in nutrient and microbial compositions and integration with NMs structure-property relationships under different environmental and local conditions to optimize release rates and

NUE.

Current A.I. and machine learning in agriculture

A 2018 review of the use of machine learning in agriculture has classified the application areas into (a) crop management, including applications on yield prediction, disease detection, weed detection crop quality, and species recognition; (b) livestock management, including applications on animal welfare and livestock production; (c) water management (daily, weekly, or monthly evapotranspiration rates); and (d) soil management such as prediction-identification of agricultural soil properties[85] . Application of Bayesian Networks to agricultural systems has been a challenge to date however, as there is often insufficient data for computing the prior and conditional probabilities required for the network[75].

In terms of the key areas identified for improvements in crop production, process based machine learning models (e.g., the SPACSYS model[86]) for plant growth, incorporating assimilation, respiration, water and N uptake, partitioning of photosynthate and N, N-fixation for legume plants and root growth[87], are emerging and being constantly improved. With increased understanding of the processes, and the availability of intervention strategies such as precision nanoagrochemicals, the potential of machine learning for optimisaiton of agroecosystems has never been higher; integrating machine learning, simulation, and portfolio optimization can inform decisions and support selection of optimal seed (e.g., soybean) varieties to grow with resolution at the level of a specific farm with its individual crop rotation history rather than at regional scale based on soil type and quality [88]. Indeed, a very recent review of the potential impacts of A.I. on the achievement of the UN sustainable development goals (SDGs) suggested that A.I. will be an enabler for SDG2 on sustainable agriculture, but highlights generally that the pace of development of A.I. may have implications in terms of a lack of regulatory oversight and insight, which could potentially result in gaps in transparency, safety, and ethical standards[89].

Nanoinformatics models applicable to nano-enabled agriculture

The application of machine learning in NM risk assessment, and for design of "safe" and environmentally friendly NMs, is also an area of intensive research in the last few years. For example, nanoQSAR models linking specific NMs properties to uptake by, and impacts on, cells or organisms are emerging, as well as models that allow determination of surface functionalizations that enhance (or decrease), for example, protein binding and/or cellular association (as a pre-requisite for internalization[79]), and can be applied for design of targeting strategies in precision nano-agriculture. Similarly, extending advances in nanomedicine to precision nanoagriculture will facilitate the design of optimized controlled release agrochemicals[90, 91]. For example, deep learning employing an automatic data splitting algorithm and the evaluation criteria suitable for pharmaceutical formulation data was developed for the prediction of optimal pharmaceutical formulations and doses[92]. From an agricultural perspective, understanding the factors (NM, plant, soil, climate etc.) that control the release rate of active ingredients, and the factors driving transport of the carrier can influence selection of formulation parameters. Such data-driven models require significant amounts of data to train and validate them, which is certainly a barrier to their current development, although significant work is underway in the nanosafety arena broadly to develop optimized workflows for data and metadata generation (e.g. utilizing Elecronic Laboratory Notebooks), annotation with relevant ontological terms mapped to the data schema of the receiving databases and automated upload to nanosafety knowledgebases[93], which in the medium term will facilitate the aggregation, integration and re-use of nanosafety and nano-agriculture related datasets.

As noted above however, there are significant concerns regarding the safety and risk of NMs that must be addressed before their widespread intentional application to the environment can be sanctioned, and there are tight regulatory processes for approval of agrochemicals[94]. A recent review has assessed the regulation of pesticides for risk assessment and the potential use of *in silico* computer-based chemical modeling technologies to facilitate risk assessment of nano-enabled pesticides[92]. This review concluded that while quantum chemistry is an appropriate tool to characterize the structure and relative stabilities of organic compounds isomers, for studying degradation processes pathways, and *via* use of quantum descriptors for QSAR development, a reevaluation for their suitability for nano-enabled agriculture is needed.

Challenges and barriers to precision nano-agriculture

Although nanotechnology demonstrates high potential in a wide range of applications in agriculture, it is still primarily at the research stage. There are many challenges to be overcome to move this area forward from basic research to full commercial scale application. This includes lack of mechanistic understanding of the interaction at NM-plant-soil interface and NM uptake and translocation in plant vascular structure and organells; insufficient understanding of the environmental safety and human health risks of intentional NM application; lack of soil and large scale field study to demonstrate the efficacy of NMs under realistic scenarios; and an unclear balance between adoption of a new technology and the low profit margin in agriculture, and the aforementioned challenges regarding collection and harmonization of the datasets needed for development of A.I models.

Long term studies at ecosystem level under environmentally relevant conditions are currently lacking. For example, silver-, zinc- and copper-based NMs show the potential to be applied as efficient pesticides or fungicide; however, the potential impact on non-target organisms (e.g., beneficial plant rhizosphere bacteria, worms) and long term impacts on soil quality are not known. Although nanofertilizers may enhance the NUE, effects (e.g., alteration of the content of carbonhydrates, macro- or micro- nutrient) of NMs on the nutritional quality of food have been reported[95] and need to be assessed systematically and predictive models need to be established. NMs might accumulate in seeds and the potential to cause transgeneration effects[96, 97] are largely unknown. The presence of NMs may cause enhanced uptake of contaminants by plants, e.g. by binding to the NM surface and co-transport, and may amplify their adverse effects[98, 99]. Such co-effects need to be fully understood.

NMs undergo numerous transformations (physically, chemically or biologically) in soils and plants. For example, many metal based NMs such as ZnO, Cu and Ag tend to dissolve and release metal ions, which can further react with soil and plant components such as phosphate, sulfur, chloride *etc*. The original NM properties that are designed for specifc application purpose might not be maintained due to these processes. For example, antifungal NMs such as Ag NMs can be oxidized, dissolve and sufildized in soil environments either by interaction with the soil microbiome or within plants, and the antifungal property of the Ag NMs could be reduced or diminished[100]. Some transformations might release toxic components, for example, graphene oxide was reported to degrade under sunlight and relase PAH (polycyclic aromatic hydrocarbon) -like compounds which are likely to exhibit toxic properties and persist in the environment[101].

Computational tools that can predict NM transformation processes will favour the design to manipulate or even simulate directly the transformation in order to maintain the NM function or modify their impacts. However, the complexity of soil chemistry and the high responsivity of plants and their secretions into the rhizosphere increase the variability and diversty of potential NM transformations (**Figure 3**). Many factors are interlinked. For example, NM transformations are affected by the soil and plant microbiome and the excreted extracellular polymeric substances (EPS) and plant root exudates around the rhizosphere. However, plant root exudate composition and microbiome can affect each other and both may be altered due to NM exposure, which can in-turn affect the NM transformation processes. Changes to the microbiome will affect the N cycling processes in soil. Foliar applied NMs can translocated downwards to root and interact with phyllosphere components such as microorganism and leaf exudates. All of the above are also subject to further change and disruption as a result of climate changes, *e.g.,* altered CO_2 and temperatures can shift nutrient cycling, alter rates of reactions /

trasnformations, change plant susceptibility to NMs and more. Therefore, the dynamic nature of the whole system needs to be considered making this a perfect candidate for A.I. and machine learning solutions.

Compared to small molecules toxicity prediction, nanoinformaticians are used to working with smaller datasets (sometimes just a few NM variants), and use exposure concentrations and timepoints as a means to expand the dataset. Thus, evaluation of the impact of NMs on NUE in a hydrophnic system for example could evaluate a panel of 8-10 NMs and evaluate their effect alone and in combination with fertilizer at different ratios and over different timescales, and determine the N concentrations in the water, plant mass and emitted to air under controlled temperatures and CO_2 levels, which would provide a multi-factorial dataset for establishment of machine learning models to predict the NUE of a new NM, as long as its physicochemical characteristics fell within the domain of applicability of the model, i.e. at least one of the NMs in the training and test set had some overlap with the properties of the "new" NM. If the NMs were characterisered over time under the different conditions, e.g., in terms of their size, dissolution, acquired corona composition, further models predicting corona composition and NMs fate and behaviour could be build, identifying the key NMs properties and environmental factors driving the specific effect. If data on plant growth (roots, shoots) or localization of the NMs in the plants were determined, increasingly complete models of NUE versus localsiation in plants could be developed. System complexity can then be build by moving to soils for example, where the NM characterization challenges increase, but where models for the NMs environmental fate already exist, such as the NanoFASE soil-water-organism model, which predict the fate of NMs in the environment[21]. Thus, the steps will be small initially, but as the datasets and models emerge, their integration with other models and tools into overall IATA and agricultural systems models will become feasible and achievable.

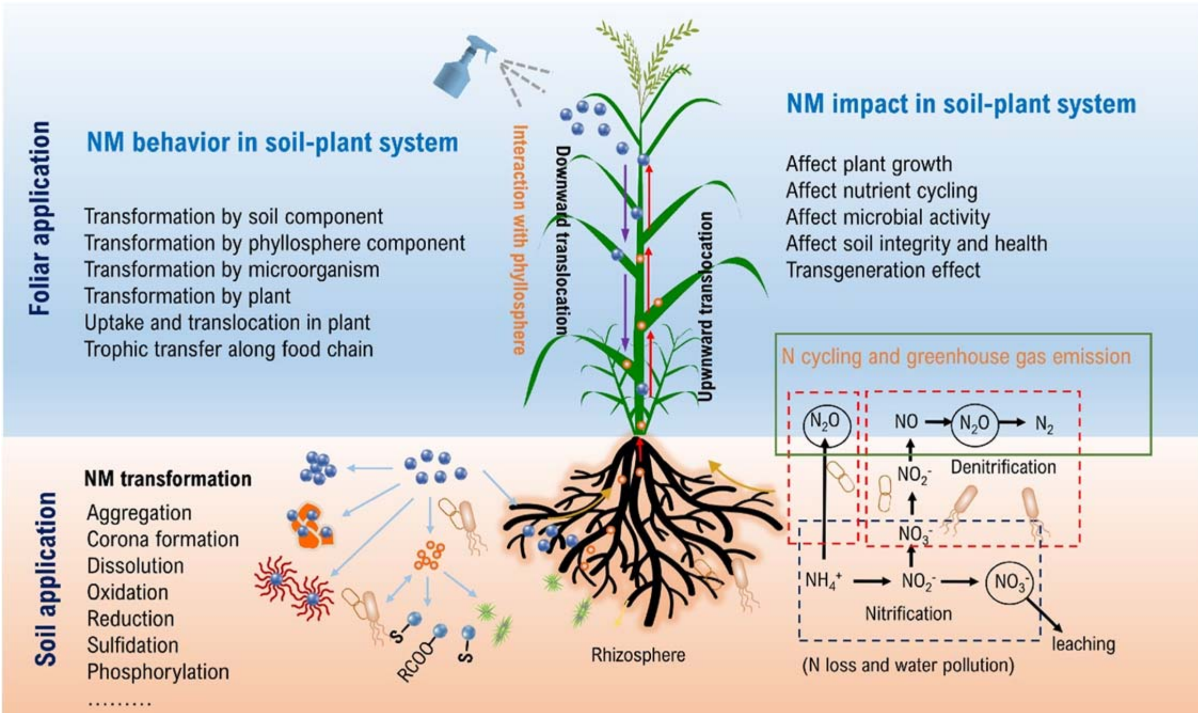

Figure 3. Schematic illustration of the complexity of NM behavior in the soil-plant environment and the potential impacts in soil-plant systems. Understanding and predicting these translocation, transformations, and identifying the optimal NMs forms to retain bioavailable N species in the soil will facilitate design of sustainably functional NMs for agriculture, enhancing NUE while simultaneously reducing pollution and the need for fertlizers. Coupling this with enhanced targeting and sustained, controlled release of pesticides can be facilitated using A.I. to design optimal nano-agrichemicals.

A roadmap for progress

Smart and nano-enabled agriculture, combined with A.I. and machine learning capability offer an exciting convergence of technologies with the unique capability to address the overarching UN SDGs, the "improved nutrition and promotion of sustainable agriculture". The impetus for smart agriculture is thus multi-pronged: from enhancing and sustaining productivity through nano-enabled (responsive) delivery of agrochemicals to crops, through to reduction in environmental pollution and negative human health impacts from agriculture. Agriculture's grand challenges can only be solved if the power of NMs can be harnessed safely, responsibly and sustainably. Nanoinformatics will play a vital role in probing the design parameters, the plant and ecosystem responses, and their co-optimising for safe and sustainable agriculture. For example, A.I. may predict NM impacts on the agricultural ecosystem and their performance in improving agricultural production (NUE, reduction in air and water pollution forms of key elements), by integrating experimental data from across different soil conditions and different plant species/climate change conditions and NM physicochemical properties, which enables safer-by-design development of nanoagricultural chemicals. Future reseach directions are outlined here to address these challenges – a summary of the future research needs is given in Box 2.

Box 2 Future research needs

- Determine the long term fate of NMs including transformation, transport in soil, uptake and translocation in plants, curate this data and its accompanying metadata into NMs-KnowledgeBases and enrich it with global soil and weather characteristics, plant biology knowledge and microbial community characteristics to facilitate development of deep learing models tailored to specific NMs being developed for nano-agriculture and the local environmental conditions.
- Assess the long term life cycle impacts of NMs in agricultural ecosystems including the trophic transfer of NMs along food chains and the potential for transgenerational impacts. Integration of these datasets into the aforementioned KnoweldgeBases will enable further iteration of the models, including development of Integrated Approaches to Testing and Assessment (IATA) and integrated agricultural systems models.
- Take a systems levels approach (as illustrated in **Figure 3**) since the whole ecosystem is interlinked with numerous co-variances, and feed this enhanced understanding into emerging regulatory frameworks.
- Utilise A.I. and machine learning to identify key nanospecific properties that initiate the adverse effects or beneficial function of NMs from large dataset obtained, thereby facilitating design of optimalised (safe-by-design) nano-agrochemicals that are fully compliant with emerging regulations.
- Integrate models addressing different aspects of the overall challenge (physics-based, process based and data driven) through alignment of input and output parameters and development of an IATA, as shown

schematically in **Figure 2**.

1) Understand the long term fate of NMs in agricultural environment including transport, transformation in soil, and uptake and translocation in plant. Transformation of NMs will change their original designed properties, which may defunctionalize their use as fertilizers, pesticides, carriers, or sensors. The transformation could occur in soil, at plant interface (e.g., root or leaf surface) and inside plant. In soil, the transformation could be driven by soil texture and chemistry, and by interaction with soil microorganisms and animals. Plant interfaces, including the rhizosphere and phyllosphere (surface of plant leaves and stems), are critical locations for NMs transformation. The dynamic and complex composition at the these regions, including plant metabolites and microorganisms, drive the transformation. NMs may also transform during their translocation in plant vascular structure by interacting with plant fluids. All these area are largely unknown.

Another critical question is how to effectively deliver NMs to target places in plant. This requires a clear understanding of the uptake and translocation of NM in plants. Both plant leaf and root have physiological barriers to prevent the entry of unwanted substances, while the structure of these two organs are very different. NMs that enter into leaf will translocate downward in phloem, while NMs entering into roots translocate upward in the xylem. The fluid composition and flow rate in xylem and phloem may greatly affect the translocation and accumulation of NMs in plant. Data and predictive models for these questions are all required urgently.

2) Assess the long term life cycle impact of NMs in agricultural ecosystem. Given the fact that repeated application of nanotechnology in agriculture is possible in the future, long term retention of NMs in agriculture soil is inevitable. The majority of the current studies regarding the plant-NMs interaction are phenomenological observations of NMs toxicity under short term, high dose conditions; long term low dose effects of NMs on agroecosystem therefore need to be studied, addressing NM impacts on plant growth, microbial acitivity and community structure, soil health (e.g., soil enzyme activity, nutrient cycling), trophic transfer of NMs and transgeneration effects.

3) Take a systems level approach to nano-enabled agriculture. The behavior, fate and impact of NMs in soil-plant system, and plant and microorganisms are all interconnected. As shown in **Figure 3** and described above, change of one factor may induce a change of the whole system. Given the power of A.I., and the complexity of the optimization challenges facing nano-agriculture, it is clear that their convergence offers exciting new directions (**Figure 4**). Utilising extensive existing models and datasets for soil quality, crop yield and NUE, for example, and combining these with models and datasets related to plant and microbial secretomes, and nanomaterials physicochemical properties, trasnformations and bioavailability, and release of active ingredients, could enable important new insights into (1) the likely transformation pathways for the NMs and their resulting environmental transport and bioavailablity; (2) the potential impact of the NM and their associated active ingredients (in cases where the NMs are carriers) on crop yield and NUE; and (3) potential identification of biomarkers of crop health / diseasae that can be utilized as early warning systems. Identification of data gaps can also drive the design of focused experiments to gap-fill or to develop sub-models to integrate into an overall model framework allowing design of NMs and active ingredient combinations that optimize NUE and minimize pollution whilst enhancing crop yield and potentially even nutritional (calorific) value. Integration of safe-by-design approaches, and feeding forward the emerging knowledge into updating of regulatory process for advanced nano-enabled agricultural applications, both in fertilization and in plant protection is essential also.

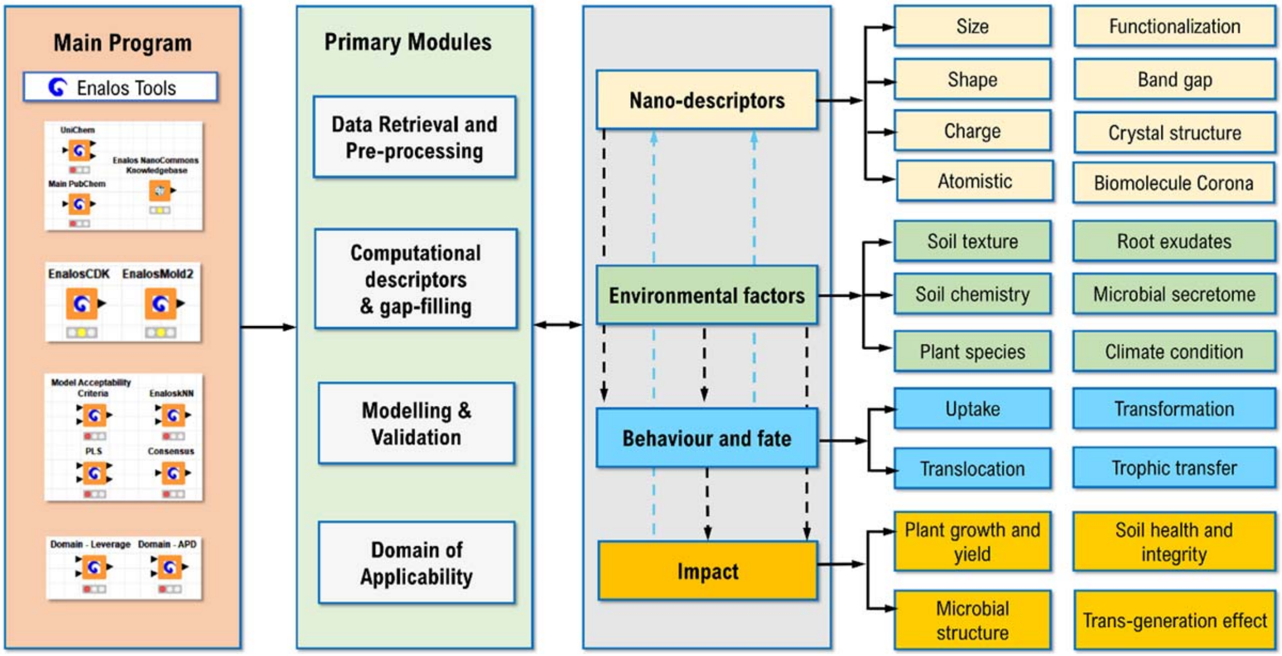

Figure 4. Approach to integration of A.I. models needed to assess ENMs behavior, fate and impact in agriculture based on the interplay between ENM and environmental factors including the crop type and soil characteristics. Integration of automated tools for harvesting data from public databases, preprocessing and curation of the data for direct input into the AI/ML models, for example via the Enalos Tools[102] in KNIME, ensures that the output data from one model can serve as the input data for subsequent models, thereby facilitating model integration and development of increasingly multiplexed predictions for nano-enabled precision agriculture.

4) Utilise A.I. and machine learning to identify key nanospecific properties that initiate the adverse effects or beneficial function of NMs from large datasets obtained through use of automated data retrieval from public databases, data pre-processing and gap-fillling, and data splitting into tets and validateion sets for modelling[102] (Figure 4). There are multiple physicochemical properties of NMs such as size, shape, surface charge, surface area, surface reactivity and crystal structure that can influence their transformations and toxicity. A.I. and machine learning will enable the selection of the most critical parameters that determine the behavior and and the prediction of the behavior of NMs in

soil and plant systems and facilitate the design of NMs that can be delivered to plants efficiently. NM transformation in different soil conditions and different root rhizosphere compositions under changing climate conditions, could be also predicted by integrating predictive models which allowing optimization of NMs for agricultural application in a range of climatic and local conditions. Wider ecosystems effects, and prediction of tripartite (NMs-soil-plant) behaviours under future climate scenarios can also be predicted, utilizing for example Baysian networks. Such models are especially important as they can operate under data scarcity, yet can easily incorporate new data as it emerges. Application of such models to address the broader issues of food security, and to tacking thhe sustainable development goal of "improved nutrition and promote sustainable agriculture" (SDG2) will provide important new intersectional insights and suggestions for ways forward.

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Author contributions

P.Z. and I.L. framed the manuscript. P.Z., Z.G., S.U. and I.L. wrote the masnucript with contributions and inputs from all authors. P.Z., A.A. and G.M. produced the graphics.

Conflict of interests

There are no conflicts of interest to declare.

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