UNIVERSITY^{OF} BIRMINGHAM University of Birmingham Research at Birmingham

Nanotechnology and artificial intelligence to enable sustainable and precision agriculture

Zhang, Peng; Guo, Zhiling; Ullah, Sami; Melagraki, Georgia; Afantitis, Antreas; Lynch, Iseult

DOI: 10.1038/s41477-021-00946-6

License: Other (please specify with Rights Statement)

Document Version Peer reviewed version

Citation for published version (Harvard):

Zhang, P, Guo, Z, Ullah, S, Mèlagraki, G, Afantitis, A & Lynch, I 2021, 'Nanotechnology and artificial intelligence to enable sustainable and precision agriculture', *Nature Plants*, vol. 7, no. 7, pp. 864–876. https://doi.org/10.1038/s41477-021-00946-6

Link to publication on Research at Birmingham portal

Publisher Rights Statement:

Zhang, P., Guo, Z., Ullah, S. et al. Nanotechnology and artificial intelligence to enable sustainable and precision agriculture. Nat. Plants (2021). https://doi.org/10.1038/s41477-021-00946-6

This document is subject to Springer Nature re-use terms: https://www.springer.com/gp/open-access/publication-policies/aam-terms-of-use

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

•Users may freely distribute the URL that is used to identify this publication.

•Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.

•User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?) •Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

1 Nanotechnology and Artificial Intelligence to Enable Sustainable and

2 **Precision Agriculture**

3 Peng Zhang¹*, Zhiling Guo¹, Sami Ullah¹, Georgia Melagraki², Antreas Afantitis² and Iseult Lynch¹

¹School of Geography, Earth and Environmental Sciences, University of Birmingham, Edgbaston,

5 Birmingham B15 2TT, UK

⁶ ²Nanoinformatics Department, Novamechanics Ltd, Nicosia, 1065, Cyprus

7 Correspondance should be addressed to P. Z. *Email: p.zhang.1@bham.ac.uk

8

9 Abstract

10 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 11 12 new approaches and integration of knowledge from diverse fields, such as materials science and 13 informatics. The convergence of precision agriculture, whereby farmers respond in real-time to changes 14 in crop growth, with nanotechnology and artificial intelligence offers exciting opportunities for 15 sustainable food production. Coupling existing models for nutrient cycling and crop productivity with 16 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 17 18 optimal safety and functionality profiles.

- 19
- 20
- 21
- 22
- 23
- 24

25 Introduction

The Green Revolution, i.e. the 3rd Agricultural Revolution, which occurred between the 1950s and 26 27 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 28 29 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, 30 31 declining soil health and fertility, low use efficiency of agrochemicals due mainly to excessive use of 32 fertilizes and pesticides, shrinking arable land *per capita* and diminishing freshwater availability for irrigation¹. Moreover, climate change, as arising from increasing atmospheric CO₂ concentration 33 leading to rising temperature, is likely to further affect the resilience of agricultural soils and their 34 ability to sustain productivity and ensure food security for an increasing human population². 35 36 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 37 crop nutrition and smart plant sensors^{3, 4, 5}. Using nanotechnology, the delivery of fertilizer⁶ can be 38 tailored by targeting to specific tissues / organisms and stimuli-responsive release, as well as 39 potentially improving nutrient use efficiency (NUE) by releasing the nutrient slowly for plant uptake⁷. 40 Nano-enabled agriculture is expected to target pests more efficiently using lower amounts of pesticide⁸ 41 42 thereby avoiding widespread impacts on soil health and biodiversity, and improving soil function and nutrient cycling via soil microbiome enhancement (optimization of nitriving/denitrifying bacterial 43 44 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 stress⁹. As 45 46 with all new technologies however, the risks must be evaluated in parallel with the benefits, and indeed 47 several NMs have been identified to cause negative changes in soil community structure, e.g. TiO₂ NMs cascading negative effects on denitrification enzyme activity and a deep modification of the 48

bacterial community structure after just 90 days of exposure to a realistic concentration of NPs (1 mg 49 kg^{-1} dry soil)¹⁰, while studies with Ag NMs, which are well-known for their antimicrobial activity have 50 51 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 NMs¹¹. Thus, an 52 important caveat at the outset of this review is that NMs represent a very broad spectrum of 53 chemistries, compositions and physicochemical properties, which are dynamic and evolving as the 54 55 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. 56

However, as noted in the aforementioned reviews^{3, 4, 5}, the development of nanotechnology for 57 agricultural applications is still at an early stage and is moving forward quite slowly. Significant 58 differences may exist between nanotechnology-based pesticides and conventional pesticides, including 59 altered bioavailability, sensitivity, dosimetry, and pharmacokinetics^{12, 13}. Challenges and barriers 60 include limited understanding of plant-NMs interactions, limited methods for efficient delivery of NMs 61 to plants and soil, risks of potentially hazardous effects of NMs to human health from accumulation of 62 NMs and active ingredient residues in edible portions of plants⁴, and to long term soil quality and soil 63 64 health from accumulation of NMs and their degradation products in soil and resultant potential alterations in microbial biodiversity¹⁴. There is an urgent need to address these barriers and achieve a 65 66 true win-win scenario, whereby improved agricultural production, reduced environmental pollution 67 from agriculture and lower costs for farmers can be achieved synergistically. A one-health approach to 68 nano-agriculture was proposed by Lombi et al., that requires interdisciplinarity and the bridging of human and environmental health research¹⁵. Computational approaches including artificial intelligence 69 70 (A.I.) and machine learning (M.L.) modelling will undoubtedly play critical roles in the progess of 71 nano-enabled agriculture, and are already starting to gain regulatory acceptance for NMs safety 72 assessment.

The application of computers and artificial intelligence (A.I.) in agriculture is not new – for 73 example, articles addressing software for integrated resource management¹⁶, image digitization for soil 74 and crop science¹⁶, and light and temperature monitoring and control for plants¹⁷ were published 35 75 76 years ago! The rise of remote sensing and integration of remote sensing data into decision support tools 77 for contemporary farming systems is expected to improve yield production and management while reducing operating costs and environmental impact¹⁸. Agricultural systems models have emerged over 78 79 the last 50 years, spanning field, farm, landscape, regional, and global spatial scales and engaging 80 questions in past, current, and future time periods. Integrated agricultural systems models combining 81 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 implementation¹⁹. 82 83 However, the comvergence of A.I. approaches and nano-enabled agriculture is in its infancy and as 84 such the current perspective aims to stimulate the development of this important area.

85 The rapid pace of the development of nanotechnologies, the enormous diversity of physico-86 chemical properties of NMs and their dynamic interactions with, and transformations, by their surroundings (e.g., corona formation, dissolution, sulfidation etc.^{20, 21}) leads to the need for *in silico* 87 88 approaches to predict and assess their safety²². 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}, 89 ²⁴. Nanoinformatics emerged a decade ago in the context that development and implementation of 90 91 nanotechnology in the real world requires the harnessing of information at the nexus of environmental 92 and human safety, risk assessment and management, physiochemical properties and function. With A.I. and M.L. enabled *in silico* risk assessment²⁵, NMs grouping and classification²⁶, and safe-by-design²⁷ 93 NMs design, as well as for predictions of NMs corona formation²⁸ and consequences for cellular 94 attachment and uptake^{29, 30, 31}, nanoinformatics has played significat roles in the area of nanosafety and 95 96 nanomedicine, while there is also ample scope of nanoinformatics in nano-enabled agriculture that has

97 not been explored, including for prediction of NMs interactions with and impacts on rhizosphere 98 secretions, NMs transformations before and during uptake and translocation, NMs impacts on soil 99 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 100 101 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 NanoSolveIT³⁵. Coupling these 102 approaches with existing models for nutrient cycling³⁶, NUE³⁷ and crop productivity³⁸ and the 103 104 aforementioned agricultural systems models into an overall Integrated Approach for Testing and 105 Assessment (IATA) will allow co-optimisation of NMs for use in agricultural systems that combine 106 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.

114

115 **Current challenges in agriculture**

With an ever increasing human population under a decreasing per capita agricultural land globally³⁹, 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 121 fertilizer use culture thus poses a serious threat to environmental quality as large amounts of nutrients 122 123 are lost into water and air causing eutrophication and greenhouse effects. For example, agriculture contributes nearly 11% of global greenhouse gas emissions⁴². Nitrogen (N) and phosphorus (P) 124 125 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 environment⁴³. Rockstrom et al. 126 recommended a reduction of reactive N use in agriculture from 150 Mt N y⁻¹ to about 35 Mt N y⁻¹ 127 globally to ensure sustainability⁴³. Such a reduction can only be achieved through a combination of 128 129 approaches including targeted nano-enabled delivery of fertilizer to match plant demands to avoid 130 excessive losses, development and availability of low-cost in situ nutrient sensing technology to help 131 farmers plan fertilization efficiently, introduce rotations into agriculture to recover the health and 132 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 N₂ directly or thorugh 133 134 enhance symbiosis are some of the key measures to enhance NUE, reduce excessive fertilization and the subsequent losses of reactive N from cultivated soil⁴⁴. Unlike N, available terrestrial P reserves are 135 136 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 era⁴³. This unsustainable use of P fertilizer in 137 agriculture is thus posing a risk to global food security⁴⁵, while causing eutrophication of fresh and 138 coastal water bodies, together with N⁴¹. 139

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 achieved⁴⁶. Recent efforts to enhance NUE include utilization of biofertilization to enhance microbial biodiversity⁴⁷, 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 imagery⁴⁸. 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 productivity⁴³.

151 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 152 microbial diseases and pest damage also cause 34% of crop loss ⁴⁹. The application of synthetic 153 154 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 retention⁵⁰; 155 156 however, these agrochemicals, which are designed to kill, also cause severe adverse impacts on the 157 health of human and non-targeted organisms and soil fertility, and result in contamination of water, soil and air⁵¹. Mis-use of agrichemicals on poor quality soils, soil degradation as a result of farming 158 159 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 160 atmospheric CO₂ levels and increasing temperatures also potentially impact the future of agriculture.⁵³ 161

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 agrochemicals that combine optimal

168 safety and functionality profiles and implementation of nano-agrichemicals into mainstream 169 agricultural systems management.

170

171 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.



179

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.

184

185 Increasing crop yields and production rates

186 The Green Revolution relied highly on the traditional agronomic factors including use of synthetic 187 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.

192 One promising way to enhance crop yield is using 'plant nanobionics', a recently coined term 193 referring to the approach of designing NMs to interact with plants in order to enhance native functions or to give the plant non-native functions⁹. A key focus is to improve the efficiency of photosynthesis, 194 195 an essential process occurring in plant leaves which uses solar energy to produce sugar from CO₂ and 196 water for plant growth. Photosynthesis efficiency can be enhanced by improving the efficiency of the 197 photosynthetic enzyme ribulose-1,5-bisphos-phate carboxylase/oxygenase (RuBisCO). A pioneering 198 study found that TiO₂ NMs promote the photosynthesis rate by activating the RuBisCO carboxylation process, potentially the result of the photocatalytic activity of TiO₂ NMs⁵⁴. More recently, root 199 200 application of carbon dots (CDs) was found to enhance RuBisCO activity thus improving the photosynthesis efficiency and carbonhydrate production in Arabidopsis thaliana⁵⁵, leading to 20% 201 202 increase of plant yield; this enhancement of plant growth was also demonstrated for several other plant 203 species such as soybean, tomato and eggplant. The overlapping adsorption of CDs with chloroplasts at 204 $420 \sim 700$ nm and the photo-induced electron donating and accepting properties of CDs are considered 205 to contribute to the enhanced photosynthesis efficiency. Other NMs, such as multiwalled carbon nanotubes (MWCNTs)⁵⁶ and CeO₂ NMs have also shown potential for improving plant phtosynthesis 206 under stress conditions^{57, 58}. CeO₂ NMs can scavenge free radicals such as hydroxyls in mesophyll cells 207 208 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 $400 \sim 700$ nm with energy conversion efficiency less than 4%. Single walled carbon nanotubes (SWCNTs) are capable of

212 capturing a broad range of solar light covering ultraviolet, green and near-infrared. Seminal work by 213 Giraldo et al. found that SWCNTs can insert into the thylakoid membrane, and that the formed 214 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 SWCNTs⁹. Using SWCNTs as a 215 carrier also enabled gene-delivery into chloroplast, a structure that is hard to target using current (often 216 liposome-based) methods⁵⁹, to improve light capture efficiency. The nanotubes also prevented the non-217 218 native DNA from integrating into the plant genome thus avoiding consumer concerns over genetically 219 modified crops. Importantly, the delivery efficiency is plant species independent and may help with 220 high-throughput screening of plants to identify phenotypes with desired functions, e.g., optimised 221 photosynthesis efficiency. For example, it could facilitate the engineering of C3 crops (e.g., rice, wheat) 222 to use the C4 pathway (e.g., maize), which have nearly 50% higher light use efficiency and higher N 223 and water use efficiency than C3 pathway plants.

224

225 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 226 227 resources whilst reducing agricultural derived environmental pollution, which is one of the main pillars 228 of the sustainable vision. Crop yield is highly dependent on external inputs of N, P and potassium (K) 229 and micronutrients (e.g., B, Fe, Mn, Cu, Zn) into the agricultural land. The overall NUE by plants currently stands at less than 50% globaly⁴⁰, with the rest retained in soil, leached into water, or emited 230 231 into air, causing detrimental environmental impacts. Engineered NMs offers great opportunity to 232 improve NUE via nano-based smart delivery platforms, i.e. so-called controlled release and targeted delivery for efficient plant uptake⁶⁰, or through NM influence on microbial communities and their 233 nitrogen fixing abilities⁵⁵. For example, using hydroxyapatite nanoneedles as carriers of urea can 234 235 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 236 the air.⁶ Such a system could also deliver pesticide active ingredients more efficiently thus reducing the 237 238 amount of pesticides needed. For example, nano copper pesticides show four orders higher efficacy against bacterial blight on pomegranate at 10⁴ times lower concentrations than that recommended for 239 copper oxychloride⁶¹. Nanotechnology also allows the nutrients or pesticides to be delivered only at the 240 241 target position, such as the plant rhizosphere. These strategies reduce the use of fertilizers and 242 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 243 agrochemicals. Lowry et al.⁴ also pointed out that selective removal or recovery of nutrients from 244 245 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 246 abundance⁶², thus could potentially be used to intentionally alter the singaling and community structure 247 248 of microbiome (e.g., N fixating bacteria) to enhance the availability of nutrients to plants. It is also 249 possible to increase the population of beneficial symbiotic bacteria (endophyte) to enhance crop 250 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 involved⁶³. One primising approach 251 to address these knowledge gaps, and facilitate development of initial A.I. models, could be soilless 252 growth systems such as hydroponics⁶⁴, where introduction plant growth-promoting rhizobacteria and 253 254 use of multi-element sensors and interpretation algorithms based on machine learning logic to monitor 255 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 256 257 soil systems.

258

259 Improving management of soil health and plant growth

260 Nanotechnology can also enable smart sensing of undesirable ambient biotic (plant pathogens, weed 261 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 262 263 agronomy. Nanotechnology based approaches for monitoring plant stress and resource deficiencies has been recently reviewed by Giraldo et al⁵. For example, the secretome of microbes, fungi, rhizosphere 264 265 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 266 inventories of secreted proteins under normal, biotic and abiotic stress conditions revealed several 267 268 different types of novel secreted proteins, such as leaderless secretory proteins potentially involved in 269 the defense/stress responses, which could be explored (including computationally, see later sections for details) for use as biomarkers⁶³. Molecule specific NMs-based sensors could be designed to detect 270 271 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, 272 especially if coupled with stimuli-responsive release^{67, 68}. Stimuli responsive sensing systems can 273 274 deliver agrochemicals only when it is necessary in response to environmental changes such as shortage 275 of nutrients, extreme pH conditions, elevated temperature or CO₂. These strategies will greatly improve 276 agronomic management and resilience of agroecosystems to stress, especially under changing climate 277 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 agrochemicals⁶⁸. 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.

286 While in terms of both risk and application of NMs, current studies in the lab, mesocosms and 287 field are expensive, time-consuming and complicated, limiting the range of conditions that can be 288 varied systematically. Results are often hard to conclude because the interpretation of the results is 289 influenced by factors such as experimental procedures, protocols, duration, NMs types, doses, soil 290 types and plant species. Integrating of the existing data, albeit with gaps and limitations, and 291 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 292 offer exciting new directions; development of a nano-agriculture IATA case study utilsiing the OECD 293 IATA case study approach⁷³ to seems like a logical next step (**Figure 2**). 294



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 nanoenabled agriculture.

301

302 A.I. and machine learning for agronomy

303 A.I. and machine learning approaches

304 As computer power increases, and the value of data as knowledge to be exploited is realized more and 305 more, A.I. and machine or deep learning approaches are emerging as means to identify patterns in large 306 datasets that are predicitve of future outcomes. One of the most widely used approaches involves neural 307 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 308 309 evaluated to ensure that they could not arise randomly. The size and range of the dataset used to train 310 the model provides the limits to its predictive power, or its domain of applicability – models cannot 311 predict reliably outside their range of data. Box 1 describes the various types of data-driven machine 312 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) 313 Relationship models (QSARs / QPARs)⁷⁴, and Bayesian Networks (BNs) which are a powerful tool for 314 incorporating uncertainty into decision support systems⁷⁵, by providing a basis for probabilistic 315 inference and facilitating assessment of changes in probabilistic belief as new evidence is entered into 316 317 the model. The larger the dataset available to train a machine learning model, the more powerful it will 318 be - typically in drug discovery or chemoinformatics for example, models will utilize data from 319 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 plants⁷⁶. Box 1. The main types of Machine Learning algorithms, and examples of their application in agriculture and/or nanomaterials design and safety assessment⁷⁷

• **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 -33and -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 toxicity⁷⁹.

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 transformations 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 imageprocessing 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 data⁸⁰, 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 suspension⁸¹.

Potential applications in nano-enabled agriculture: could be applied to prediction of NMs transformations under different soil and climate conditions; for prediction and clustering of efficacy of nano-enabled agrichemicals 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 environment⁸².

Applications in NMs deisgn, safety and interactions: A recent example used Kohonen networks⁸³, 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 toxicity⁸⁴.

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.

323

324 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 properties⁸⁵. 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 network⁷⁵.

In terms of the key areas identified for improvements in crop production, process based 332 machine learning models (e.g., the SPACSYS model⁸⁶) for plant growth, incorporating assimilation, 333 334 respiration, water and N uptake, partitioning of photosynthate and N, N-fixation for legume plants and root growth⁸⁷, are emerging and being constantly improved. With increased understanding of the 335 336 processes, and the availability of intervention strategies such as precision nanoagrochemicals, the 337 potential of machine learning for optimisaiton of agroecosystems has never been higher; integrating 338 machine learning, simulation, and portfolio optimization can inform decisions and support selection of 339 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 340 341 very recent review of the potential impacts of A.I. on the achievement of the UN sustainable 342 development goals (SDGs) suggested that A.I. will be an enabler for SDG2 on sustainable agriculture, 343 but highlights generally that the pace of development of A.I. may have implications in terms of a lack 344 of regulatory oversight and insight, which could potentially result in gaps in transparency, safety, and ethical standards⁸⁹. 345

346 Nanoinformatics models applicable to nano-enabled agriculture

The application of machine learning in NM risk assessment, and for design of "safe" and 347 348 environmentally friendly NMs, is also an area of intensive research in the last few years. For example, 349 nanoQSAR models linking specific NMs properties to uptake by, and impacts on, cells or organisms 350 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 351 internalization⁷⁹), and can be applied for design of targeting strategies in precision nano-agriculture. 352 Similarly, extending advances in nanomedicine to precision nanoagriculture will facilitate the design of 353 optimized controlled release agrochemicals^{90, 91}. For example, deep learning employing an automatic 354 355 data splitting algorithm and the evaluation criteria suitable for pharmaceutical formulation data was developed for the prediction of optimal pharmaceutical formulations and doses⁹². From an agricultural 356 357 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 358 359 parameters. Such data-driven models require significant amounts of data to train and validate them, 360 which is certainly a barrier to their current development, although significant work is underway in the 361 nanosafety arena broadly to develop optimized workflows for data and metadata generation (e.g. 362 utilizing Elecronic Laboratory Notebooks), annotation with relevant ontological terms mapped to the data schema of the receiving databases and automated upload to nanosafety knowledgebases⁹³, which 363 364 in the medium term will facilitate the aggregation, integration and re-use of nanosafety and nano-365 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 agrochemicals⁹⁴. A recent review has assessed the regulation of pesticides for risk assessment and the potential use of *in silico* computerbased chemical modeling technologies to facilitate risk assessment of nano-enabled pesticides⁹². 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.

375

376 Challenges and barriers to precision nano-agriculture

377 Although nanotechnology demonstrates high potential in a wide range of applications in agriculture, it 378 is still primarily at the research stage. There are many challenges to be overcome to move this area 379 forward from basic research to full commercial scale application. This includes lack of mechanistic 380 understanding of the interaction at NM-plant-soil interface and NM uptake and translocation in plant 381 vascular structure and organells; insufficient understanding of the environmental safety and human 382 health risks of intentional NM application; lack of soil and large scale field study to demonstrate the 383 efficacy of NMs under realistic scenarios; and an unclear balance between adoption of a new 384 technology and the low profit margin in agriculture, and the aforementioned challenges regarding 385 collection and harmonization of the datasets needed for development of A.I models.

386 Long term studies at ecosystem level under environmentally relevant conditions are currently 387 lacking. For example, silver, zinc- and copper-based NMs show the potential to be applied as efficient 388 pesticides or fungicide; however, the potential impact on non-target organisms (e.g., beneficial plant 389 rhizosphere bacteria, worms) and long term impacts on soil quality are not known. Although 390 nanofertilizers may enhance the NUE, effects (e.g., alteration of the content of carbonhydrates, macroor micro- nutrient) of NMs on the nutritional quality of food have been reported⁹⁵ and need to be 391 392 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 393

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.

396 NMs undergo numerous transformations (physically, chemically or biologically) in soils and 397 plants. For example, many metal based NMs such as ZnO, Cu and Ag tend to dissolve and release 398 metal ions, which can further react with soil and plant components such as phosphate, sulfur, chloride 399 etc. The original NM properties that are designed for specifc application purpose might not be 400 maintained due to these processes. For example, antifungal NMs such as Ag NMs can be oxidized, 401 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 diminished¹⁰⁰. Some 402 403 transformations might release toxic components, for example, graphene oxide was reported to degrade 404 under sunlight and relase PAH (polycyclic aromatic hydrocarbon) -like compounds which are likely to exhibt toxic properties and persist in the environment¹⁰¹. 405

406 Computational tools that can predict NM transformation processes will favour the design to 407 manipulate or even simulate directly the transformation in order to maintain the NM function or modify 408 their impacts. However, the complexity of soil chemistry and the high responsivity of plants and their 409 secretions into the rhizosphere increase the variability and diversty of potential NM transformations 410 (Figure 3). Many factors are interlinked. For example, NM transformations are affected by the soil and 411 plant microbiome and the excreted extracellular polymeric substances (EPS) and plant root exudates 412 around the rhizosphere. However, plant root exudate composition and microbiome can affect each 413 other and both may be altered due to NM exposure, which can in-turn affect the NM transformation 414 processes. Changes to the microbiome will affect the N cycling processes in soil. Foliar applied NMs 415 can translocated downwards to root and interact with phyllosphere components such as microorganism 416 and leaf exudates. All of the above are also subject to further change and disruption as a result of 417 climate changes, e.g., altered CO₂ and temperatures can shift nutrient cycling, alter rates of reactions /

418 trasnformations, change plant susceptibility to NMs and more. Therefore, the dynamic nature of the 419 whole system needs to be considered making this a perfect candidate for A.I. and machine learning 420 solutions.

421 Compared to small molecules toxicity prediction, nanoinformaticians are used to working with 422 smaller datasets (sometimes just a few NM variants), and use exposure concentrations and timepoints 423 as a means to expand the dataset. Thus, evaluation of the impact of NMs on NUE in a hydrophnic 424 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 425 426 concentrations in the water, plant mass and emitted to air under controlled temperatures and CO₂ 427 levels, which would provide a multi-factorial dataset for establishment of machine learning models to 428 predict the NUE of a new NM, as long as its physicochemical characteristics fell within the domain of 429 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 430 431 conditions, e.g., in terms of their size, dissolution, acquired corona composition, further models 432 predicting corona composition and NMs fate and behaviour could be build, identifying the key NMs 433 properties and environmental factors driving the specific effect. If data on plant growth (roots, shoots) 434 or localization of the NMs in the plants were determined, increasingly complete models of NUE versus 435 localsiation in plants could be developed. System complexity can then be build by moving to soils for 436 example, where the NM characterization challenges increase, but where models for the NMs 437 environmental fate already exist, such as the NanoFASE soil-water-organism model, which predict the fate of NMs in the environment²¹. Thus, the steps will be small initially, but as the datasets and models 438 439 emerge, their integration with other models and tools into overall IATA and agricultural systems 440 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.

448

441

449 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 456 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 457 458 sustainable agriculture. For example, A.I. may predict NM impacts on the agricultural ecosystem and 459 their performance in improving agricultural production (NUE, reduction in air and water pollution 460 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 461 462 safer-by-design development of nanoagricultural chemicals. Future reseach directions are outlined here 463 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 nanoagriculture 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**.

464 1) Understand the long term fate of NMs in agricultural environment including transport, 465 transformation in soil, and uptake and translocation in plant. Transformation of NMs will change their 466 original designed properties, which may defunctionalize their use as fertilizers, pesticides, carriers, or 467 sensors. The transformation could occur in soil, at plant interface (e.g., root or leaf surface) and inside 468 plant. In soil, the transformation could be driven by soil texture and chemistry, and by interaction with 469 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 470 471 composition at the these regions, including plant metabolites and microorganisms, drive the 472 transformation. NMs may also transform during their translocation in plant vascular structure by 473 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. 488 3) Take a systems level approach to nano-enabled agriculture. The behavior, fate and impact of 489 NMs in soil-plant system, and plant and microorganisms are all interconnected. As shown in Figure 3 490 and described above, change of one factor may induce a change of the whole system. Given the power 491 of A.I., and the complexity of the optimization challenges facing nano-agriculture, it is clear that their 492 convergence offers exciting new directions (Figure 4). Utilising extensive existing models and datasets 493 for soil quality, crop yield and NUE, for example, and combining these with models and datasets 494 related to plant and microbial secretomes, and nanomaterials physicochemical properties, 495 trasnformations and bioavailability, and release of active ingredients, could enable important new 496 insights into (1) the likely transformation pathways for the NMs and their resulting environmental 497 transport and bioavailablity; (2) the potential impact of the NM and their associated active ingredients 498 (in cases where the NMs are carriers) on crop yield and NUE; and (3) potential identification of 499 biomarkers of crop health / diseasae that can be utilized as early warning systems. Identification of data 500 gaps can also drive the design of focused experiments to gap-fill or to develop sub-models to integrate 501 into an overall model framework allowing design of NMs and active ingredient combinations that 502 optimize NUE and minimize pollution whilst enhancing crop yield and potentially even nutritional 503 (calorific) value. Integration of safe-by-design approaches, and feeding forward the emerging 504 knowledge into updating of regulatory process for advanced nano-enabled agricultural applications, 505 both in fertilization and in plant protection is essential also.



507

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 Tools¹⁰² 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.

515

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-filling, and data splitting into tets and validateion sets for modelling¹⁰² (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 523 soil and plant systems and facilitate the design of NMs that can be delivered to plants efficiently. NM 524 transformation in different soil conditions and different root rhizosphere compositions under changing 525 climate conditions, could be also predicted by integrating predictive models which allowing 526 optimization of NMs for agricultural application in a range of climatic and local conditions. Wider 527 ecosystems effects, and prediction of tripartite (NMs-soil-plant) behaviours under future climate 528 scenarios can also be predicted, utilizing for example Baysian networks. Such models are especially 529 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 530 531 sustainable development goal of "improved nutrition and promote sustainable agriculture" (SDG2) will 532 provide important new intersectional insights and suggestions for ways forward.

533

534 Acknowledgements

535 IL, AA and GM acknowledge funding from the EU H2020 projects RiskGone (Grant Agreement N^o 536 814425), NanoSolveIT (Grant Agreement N^o 814572) and NanoCommons (Grant Agreement N^o 537 731032). IL, PZ and ZG acknowledge support from the UoB Institute for Global Innovation 538 Environmental Pollution Solutions theme.

539

540 Author contributions

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

543

544 **Conflict of interests**

545 There are no conflicts of interest to declare.

546

547 **References**

550

553

556

559

562

565

569

572

575

579

- Shahzad, A. N., Qureshi, M. K., Wakeel, A., Misselbrook, T. Crop production in Pakistan and low nitrogen use efficiencies. *Nat. Sustain.* 2, 1106-1114 (2019).
- 551 2. He, W., Yoo, G., Moonis, M., Kim, Y., Chen, X. J. P. Impact assessment of high soil CO₂ on 552 plant growth and soil environment: a greenhouse study. *Peer J.* **7**, e6311 (2019).
- 554 3. Kah, M., Tufenkji, N., White, J. C. Nano-enabled strategies to enhance crop nutrition and 555 protection. *Nat. Nanotechnol.* **14**, 532-540 (2019).
- 4. Lowry, G. V., Avellan, A., Gilbertson, L. M. Opportunities and challenges for nanotechnology in the agri-tech revolution. *Nat. Nanotechnol.* **14**, 517-522 (2019).
- 560 5. Giraldo, J. P., Wu, H., Newkirk, G. M., Kruss, S. Nanobiotechnology approaches for 561 engineering smart plant sensors. *Nat. Nanotechnol.* **14**, 541-553 (2019).
- 563 6. Kottegoda, N., *et al.* Urea-hydroxyapatite nanohybrids for slow release of nitrogen. *ACS Nano*564 **11**, 1214-1221 (2017).
- Kabiri, S., Degryse, F., Tran, D. N., da Silva, R. C., McLaughlin, M. J., Losic, D. Graphene
 oxide: A new carrier for slow release of plant micronutrients. ACS Appl. Mat. Interfaces 9, 43325-43335 (2017).
- 570 8. Huang, B., *et al.* Advances in targeted pesticides with environmentally responsive controlled
 571 release by nanotechnology. *Nanomaterials* 8, 102 (2018).
- 573 9. Giraldo, J. P., *et al.* Plant nanobionics approach to augment photosynthesis and biochemical sensing. *Nat. Mat.* **13**, 400-408 (2014).
- Simonin, M., Richaume, A., Guyonnet, J. P., Dubost, A., Martins, J. M., Pommier, T. J.
 Titanium dioxide nanoparticles strongly impact soil microbial function by affecting archaeal nitrifiers. *Sci. Reports* 6, 1-10 (2016).
- 580 11. Grün, A.-L., *et al.* Impact of silver nanoparticles (AgNP) on soil microbial community
 581 depending on functionalization, concentration, exposure time, and soil texture. *Environ. Sci.*582 *Eur.* 31, 15 (2019).
- Stone, D., Harper, B. J., Lynch, I., Dawson, K., Harper, S. L. Exposure assessment:
 recommendations for nanotechnology-based pesticides. *Int. J. Occup. Environ. Health* 16, 467474 (2010).
- 588 13. Kookana, R. S., *et al.* Nanopesticides: guiding principles for regulatory evaluation of
 environmental risks. *J Agric Food Chem* 62, 4227-4240 (2014).
- 14. Richarz, A.-N., Lamon, L., Asturiol, D., Worth, A. P. J. Pitfalls. Perspectives. Current developments and recommendations in computational nanotoxicology in view of regulatory applications. Computational Nanotoxicology, Chapter 2, 99-155 (2019).

595 15. Lombi, E., Donner, E., Dusinska, M., Wickson, F. J. A One Health approach to managing the 596 applications and implications of nanotechnologies in agriculture. Nat. Nanotechnol. 14, 523-531 597 (2019). 598 599 16. Heermann, D. F., Duke, H. R., Buchleiter, G. W. 'User friendly'software for an integrated 600 water-energy management system for center pivot irrigation. Comput. Electron. Agric. 1, 41-57 601 (1985). 602 603 17. White, J. W., Hamilton, J. H. Irradiance and plant temperature monitor/controller. Comput. 604 *Electron. Agric.* 1, 95-103 (1985). 605 606 18. Chlingaryan, A., Sukkarieh, S., Whelan, B. Machine learning approaches for crop yield 607 prediction and nitrogen status estimation in precision agriculture: A review. Comput. Electron. 608 Agric. 151, 61-69 (2018). 609 610 19. Jones, J. W., et al. Toward a new generation of agricultural system data, models, and 611 knowledge products: State of agricultural systems science. Agri. Systems 155, 269-288 (2017). 612 613 Xu, L., Xu, M., Wang, R., Yin, Y., Lynch, I., Liu, S. The Crucial Role of Environmental 20. 614 Coronas in Determining the Biological Effects of Engineered Nanomaterials. Small 16, 615 2003691 (2020). 616 617 Svendsen, C., et al. Key principles and operational practices for improved nanotechnology 21. environmental exposure assessment. Nat. Nanotechnol. 15, 1-12 (2020). 618 619 620 22. Winkler, D. A. J. S. Role of Artificial Intelligence and Machine Learning in Nanosafety. Small 621 **16**, 2001883 (2020). 622 623 Burello, E., Worth, A. A theoretical framework for predicting the oxidative stress potential of 23. 624 oxide nanoparticles. Nanotoxicology 5, 228-235 (2011). 625 626 24. Karatzas, P., et al. Development of deep learning models for predicting the effects of exposure to engineered nanomaterials on Daphnia Magna. Small 16, 2001080 (2020). 627 628 629 25. Cohen, Y., Rallo, R., Liu, R., Liu, H. H. In silico analysis of nanomaterials hazard and risk. 630 Acc. Chem. Res. 46, 802-812 (2013). 631 632 26. Lamon, L., et al. Grouping of nanomaterials to read-across hazard endpoints: from data 633 collection to assessment of the grouping hypothesis by application of chemoinformatic 634 techniques. Part. Fibre Toxicol. 15, 37 (2018). 635 636 27. Varsou, D.-D., et al. A safe-by-design tool for functionalised nanomaterials through the Enalos 637 Nanoinformatics Cloud platform. Nanoscale Adv. 1, 706-718 (2019). 638 639 28. Findlay, M. R., Freitas, D. N., Mobed-Miremadi, M., Wheeler, K. Machine learning provides 640 predictive analysis into silver nanoparticle protein corona formation from physicochemical properties. Environ. Sci.: Nano 5, 64-71 (2018). 641

643 29. Duan, Y., *et al.* Prediction of protein corona on nanomaterials by machine learning using novel descriptors. *NanoImpact* 17, 100207 (2020).

642

645

649

653

657

661

664

668

671

675

679

- Ban, Z., Yuan, P., Yu, F., Peng, T., Zhou, Q., Hu, X. Machine learning predicts the functional composition of the protein corona and the cellular recognition of nanoparticles. *Proc. Natl. Acad. Sci.* 117, 10492-10499 (2020).
- Afantitis, A., Melagraki, G., Tsoumanis, A., Valsami-Jones, E., Lynch, I. nanoinformatics
 decision support tool for the virtual screening of gold nanoparticle cellular association using
 protein corona fingerprints. *Nanotoxicology* 12, 1148-1165 (2018).
- McManus, P., *et al.* Rhizosphere interactions between copper oxide nanoparticles and wheat
 root exudates in a sand matrix: Influences on copper bioavailability and uptake. *Environ. Toxicol. Chem.* 37, 2619-2632 (2018).
- 33. Zhang, P., Guo, Z., Zhang, Z., Fu, H., White, J. C., Lynch, I. Nanomaterial Transformation in the Soil–Plant System: Implications for Food Safety and Application in Agriculture. *Small* 16, 2000705 (2020).
- 662 34. Zhang, P., *et al.* Plant species-dependent transformation and translocation of ceria nanoparticles. *Environ. Sci.: Nano* **6**, 60-67 (2019).
- Afantitis, A., *et al.* NanoSolveIT Project: Driving nanoinformatics research to develop innovative and integrated tools for in silico nanosafety assessment. *Comput. Struct. Biotechnol. J.* 18, 583-602 (2020).
- 669 36. De Willigen, P., Neeteson, J. Comparison of six simulation models for the nitrogen cycle in the soil. *Fertilizer Res.* 8, 157-171 (1985).
- 672 37. Pathak, H., *et al.* Modelling the quantitative evaluation of soil nutrient supply, nutrient use
 673 efficiency, and fertilizer requirements of wheat in India. *Nutr. Cycling in Agroecosyst.* 65, 105674 113 (2003).
- Janssen, B. H. Simple models and concepts as tools for the study of sustained soil productivity
 in long-term experiments. II. Crop nutrient equivalents, balanced supplies of available nutrients,
 and NPK triangles. *Plant Soil* **339**, 17-33 (2011).
- Klein Goldewijk, K., Dekker, S. C., van Zanden, J. L. Per-capita estimations of long-term historical land use and the consequences for global change research. *J. Land Use Sci.* 12, 313-337 (2017).
- 40. Lassaletta, L., Billen, G., Grizzetti, B., Anglade, J., Garnier, J. 50 year trends in nitrogen use
 efficiency of world cropping systems: the relationship between yield and nitrogen input to
 cropland. *Environ. Res. Lett.* 9, 105011 (2014).
- 41. van Grinsven, H. J., Bouwman, L., Cassman, K. G., van Es, H. M., McCrackin, M. L., Beusen,
 A. H. Losses of ammonia and nitrate from agriculture and their effect on nitrogen recovery in

| 690 691 692 | | the European Union and the United States between 1900 and 2050. J. Environ. Qual. 44, 356-367 (2015). |
|--|------------|---|
| 693 694 695 | 42. | Burney, J. A., Davis, S. J., Lobell, D. B. Greenhouse gas mitigation by agricultural intensification. <i>Proc. Natl. Acad. Sci.</i> 107 , 12052-12057 (2010). |
| 696 697 698 | 43. | Rockström, J., et al. Planetary boundaries: exploring the safe operating space for humanity. Ecol. Soc. 14, (2009). |
| 699 700 701 | 44. | Raza, S., <i>et al.</i> Piling up reactive nitrogen and declining nitrogen use efficiency in Pakistan: a challenge not challenged (1961–2013). <i>Environ. Res. Lett.</i> 13 , 034012 (2018). |
| 702 703 704 | 45. | Cordell, D., Drangert, JO., White, S. The story of phosphorus: global food security and food for thought. <i>Global Environ. Change</i> 19 , 292-305 (2009). |
| 705 706 707 708 | 46. | Van Grinsven, H. J., Erisman, J. W., de Vries, W., Westhoek, H. Potential of extensification of European agriculture for a more sustainable food system, focusing on nitrogen. <i>Environ. Res. Lett.</i> 10 , 025002 (2015). |
| 709 710 711 | 47. | Schütz, L., <i>et al.</i> Improving crop yield and nutrient use efficiency via biofertilization—A global meta-analysis. <i>Front. Plant Sci.</i> 8 , 2204 (2018). |
| 712 713 714 | 48. | Sharma, L. K., Bali, S. K. A review of methods to improve nitrogen use efficiency in agriculture. <i>Sustainability</i> 10 , 51 (2018). |
| 715 716 | 49. | Oerke, EC. Crop losses to pests. J. Agri. Sci. 144, 31-43 (2006). |
| 717 718 719 720 | 50. | Bindraban, P. S., Dimkpa, C., Nagarajan, L., Roy, A., Rabbinge, R. Revisiting fertilisers and fertilisation strategies for improved nutrient uptake by plants. <i>Bio. Fertil. Soils</i> 51 , 897-911 (2015). |
| 721 722 723 | 51. | Aktar, W., Sengupta, D., Chowdhury, A. Impact of pesticides use in agriculture: their benefits and hazards. <i>Interdiscip. Toxicol.</i> 2 , 1-12 (2009). |
| 724 725 726 | 52. | National Academies of Sciences, E., Medicine. Science breakthroughs to advance food and agricultural research by 2030. National Academies Press (2019). |
| 720 727 728 | 53. | Parry, M. L. Climate change and world agriculture. Routledge (2019). |
| 720 | | |
| 729 730 731 | 54. | Gao, F., <i>et al.</i> Mechanism of nano-anatase TiO 2 on promoting photosynthetic carbon reaction of spinach. <i>Biol. Trace Elem. Res.</i> 111 , 239-253 (2006). |
| 729 730 731 732 733 734 | 54. 55. | Gao, F., <i>et al.</i> Mechanism of nano-anatase TiO 2 on promoting photosynthetic carbon reaction of spinach. <i>Biol. Trace Elem. Res.</i> 111, 239-253 (2006). Li, H., <i>et al.</i> Enhanced RuBisCO activity and promoted dicotyledons growth with degradable carbon dots. <i>Nano Res.</i> 12, 1585-1593 (2019). |

738 739 57. Wu, H., Shabala, L., Shabala, S., Giraldo, J. P. J. E. S. N. Hydroxyl radical scavenging by 740 cerium oxide nanoparticles improves Arabidopsis salinity tolerance by enhancing leaf 741 mesophyll potassium retention. Environ. Sci.: Nano 5, 1567-1583 (2018). 742 743 58. Wang, Y., et al. Alleviation of nitrogen stress in rice (Oryza sativa) by ceria nanoparticles. 744 Environ. Sci.: Nano https://doi.org/10.1039/D0EN00757A (2020). 745 746 59. Kwak, S.-Y., et al. Chloroplast-selective gene delivery and expression in planta using chitosan-747 complexed single-walled carbon nanotube carriers. Nat. Nanotechnol. 14, 447-455 (2019). 748 749 60. Guo, H., White, J. C., Wang, Z., Xing, B. Nano-enabled fertilizers to control the release and use 750 efficiency of nutrients. Curr. Opin. Environ. Sci. Health 6, 77-83 (2018). 751 752 61. Mondal, K. K., Mani, C. Investigation of the antibacterial properties of nanocopper against 753 Xanthomonas axonopodis py, punicae, the incitant of pomegranate bacterial blight. Ann. 754 Microbiol. 62, 889-893 (2012). 755 756 Asadishad, B., Chahal, S., Cianciarelli, V., Zhou, K., Tufenkji, N. Effect of gold nanoparticles 62. 757 on extracellular nutrient-cycling enzyme activity and bacterial community in soil slurries: role 758 of nanoparticle size and surface coating. Environ. Sci.: Nano 4, 907-918 (2017). 759 760 63. Agrawal, G. K., Jwa, N. S., Lebrun, M. H., Job, D., Rakwal, R. Plant secretome: unlocking 761 secrets of the secreted proteins. Proteomics 10, 799-827 (2010). 762 763 64. Sambo, P., et al. Hydroponic solutions for soilless production systems: Issues and opportunities 764 in a smart agriculture perspective. Front. Plant Sci. 10, 923 (2019). 765 766 65. Jung, D. H., Kim, H.-J., Choi, G. L., Ahn, T.-I., Son, J.-E., Sudduth, K. A. Automated lettuce 767 nutrient solution management using an array of ion-selective electrodes. T. ASABE 58, 1309-768 1319 (2015). 769 770 66. Girard, V., Dieryckx, C., Job, C., Job, D. Secretomes: the fungal strike force. Proteomics 13, 771 597-608 (2013). 772 773 Camara, M. C., Campos, E. V. R., Monteiro, R. A., Santo Pereira, A. d. E., de Freitas Proença, 67. 774 P. L., Fraceto, L. F. Development of stimuli-responsive nano-based pesticides: emerging 775 opportunities for agriculture. J. Nanobiotechnol. 17, 100 (2019). 776 777 68. Xu, X., Bai, B., Wang, H., Suo, Y. A near-infrared and temperature-responsive pesticide release 778 platform through core-shell polydopamine@ PNIPAm nanocomposites. ACS Appl. 779 Mat.Interfaces 9, 6424-6432 (2017). 780 781 Tian, H., Kah, M., Kariman, K. Are nanoparticles a threat to mycorrhizal and rhizobial 69. 782 symbioses? A critical review. Front. Microbiol. 10, 1660 (2019). 783 784 70. Eymard-Vernain, E., et al. Impact of a model soil microorganism and of its secretome on the 785 fate of silver nanoparticles. Environ. Sci. Technol. 52, 71-78 (2018).

- 787 71. Murphy, F., *et al.* A tractable method for measuring nanomaterial risk using Bayesian networks.
 788 *Nanoscale Res. Lett.* 11, 503 (2016).
 789
- Furxhi, I., Murphy, F., Poland, C. A., Sheehan, B., Mullins, M., Mantecca, P. Application of
 Bayesian networks in determining nanoparticle-induced cellular outcomes using
 transcriptomics. *Nanotoxicology* 13, 827-848 (2019).
- 794 73. OECD Environment Health and Safety Publications Series on Testing and Assessment No. 46.
 (2004).
- 74. Kar, S., Roy, K., Leszczynski, J. On applications of QSARs in food and agricultural sciences:
 history and critical review of recent developments. In: *Advances in QSAR Modeling*. Springer
 (2017).
- Tari, F. A Bayesian network for predicting yield response of winter wheat to fungicide
 programmes. *Comput. Electron. Agric.* 15, 111-121 (1996).
- Krouk, G., Lingeman, J., Colon, A. M., Coruzzi, G., Shasha, D. Gene regulatory networks in plants: learning causality from time and perturbation. *Genome Biol.* 14, 123 (2013).
- 807 77. Baştanlar, Y., Özuysal, M. Introduction to machine learning. In: *miRNomics: MicroRNA* 808 *Biology and Computational Analysis*. Springer (2014).
 809
- 810 78. Nemes, A., Rawls, W. J., Pachepsky, Y. A. Use of the nonparametric nearest neighbor approach
 811 to estimate soil hydraulic properties. *Soil Sci. Soc. Am. J.* **70**, 327-336 (2006).
- Afantitis, A., Melagraki, G., Tsoumanis, A., Valsami-Jones, E., Lynch, I. A nanoinformatics
 decision support tool for the virtual screening of gold nanoparticle cellular association using
 protein corona fingerprints. *Nanotoxicology* 12, 1148-1165 (2018).
- 80. Pedroso, M., Taylor, J., Tisseyre, B., Charnomordic, B., Guillaume, S. A segmentation algorithm for the delineation of agricultural management zones. *Comput. Electron. Agric.* 70, 199-208 (2010).
- 81. Bi, X., et al. Quantitative resolution of nanoparticle sizes using single particle inductively
 coupled plasma mass spectrometry with the K-means clustering algorithm. J. Anal. At.
 Spectrom. 29, 1630-1639 (2014).
- 825 82. Bu, F., Wang, X. A smart agriculture IoT system based on deep reinforcement learning. *Future*826 *Gener. Comput. Syst.* 99, 500-507 (2019).
- 828 83. Sun, B., Barnard, A. S. Visualising multi-dimensional structure/property relationships with 829 machine learning. *J. Phys.: Mat.* **2**, 034003 (2019).
- 831 84. Lamon, L., Aschberger, K., Asturiol, D., Richarz, A., Worth, A. Grouping of nanomaterials to
 832 read-across hazard endpoints: a review. *Nanotoxicology* 13, 100-118 (2019).
- 833

786

793

800

806

812

816

820

824

827

- 834 85. Liakos, K. G., Busato, P., Moshou, D., Pearson, S., Bochtis, D. Machine learning in agriculture:
 835 A review. *Sensors* 18, 2674 (2018).
- 837 86. Liang, S., Zhang, X., Sun, N., Li, Y., Xu, M., Wu, L. Modeling crop yield and nitrogen use
 838 efficiency in wheat and maize production systems under future climate change. *Nutr. Cycling*839 *Agroecosyst.* 115, 117-136 (2019).
- 841 87. Liu, Y., *et al.* Modelling field scale spatial variation in water run-off, soil moisture, N2O
 842 emissions and herbage biomass of a grazed pasture using the SPACSYS model. *Geoderma* 315, 49-58 (2018).
- 845
 88. Sundaramoorthi, D., Dong, L. Machine-Learning-Based Simulation for Estimating Parameters in Portfolio Optimization: Empirical Application to Soybean Variety Selection. *Available at SSRN 3412648*, https://dx.doi.org/10.2139/ssrn.3412648 (2019).
- 849 89. Vinuesa, R., *et al.* The role of artificial intelligence in achieving the Sustainable Development Goals. *Nat. Commun.* 11, 1-10 (2020).
 851
- 852 90. Kaddi, C. D., Phan, J. H., Wang, M. D. Computational nanomedicine: modeling of 853 nanoparticle-mediated hyperthermal cancer therapy. *Nanomedicine* **8**, 1323-1333 (2013).
- 855 91. Kumar, P., Khan, R. A., Choonara, Y. E., Pillay, V. A prospective overview of the essential requirements in molecular modeling for nanomedicine design. *Future Med. Chem.* 5, 929-946
 857 (2013).
- Yang, Y., Ye, Z., Su, Y., Zhao, Q., Li, X., Ouyang, D. Deep learning for in vitro prediction of pharmaceutical formulations. *Acta Pharm. Sin. B* 9, 177-185 (2019).
- Martinez, D. S. T., Da Silva, G. H., de Medeiros, A. M. Z., Khan, L. U., Papadiamantis, A. G.,
 Lynch, I. Effect of the Albumin Corona on the Toxicity of Combined Graphene Oxide and
 Cadmium to Daphnia magna and Integration of the Datasets into the NanoCommons
 Knowledge Base. *Nanomaterials* 10, 1936 (2020).
- 867 94. Hardy, A., *et al.* Guidance on risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain: Part 1, human and animal health. *EFSA J.* 16, (2018).
- 871 95. Zhao, L., *et al.* CeO2 and ZnO nanoparticles change the nutritional qualities of cucumber (Cucumis sativus). *J Agric. Food Chem.* 62, 2752-2759 (2014).
- Wang, Q., Ma, X., Zhang, W., Pei, H., Chen, Y. The impact of cerium oxide nanoparticles on tomato (Solanum lycopersicum L.) and its implications for food safety. *Metallomics* 4, 1105-1112 (2012).
- 878 97. Tan, W., *et al.* Effects of the exposure of TiO₂ nanoparticles on basil (Ocimum basilicum) for two generations. *Sci. Total Environ.* 636, 240-248 (2018).
- 880

836

840

844

848

854

858

861

866

870
- 881 98. Hu, X., Kang, J., Lu, K., Zhou, R., Mu, L., Zhou, Q. Graphene oxide amplifies the phytotoxicity of arsenic in wheat. *Sci. Rep.* 4, 1-10 (2014).
- Be La Torre-Roche, R., *et al.* Multiwalled carbon nanotubes and C60 fullerenes differentially
 impact the accumulation of weathered pesticides in four agricultural plants. *Environ. Sci. Technol.* 47, 12539-12547 (2013).
- Reinsch, B., *et al.* Sulfidation of silver nanoparticles decreases Escherichia coli growth
 inhibition. *Environ. Sci. Technol.* 46, 6992-7000 (2012).
- Hou, W.-C., *et al.* Photochemical transformation of graphene oxide in sunlight. *Environ. Sci. Technol.* 49, 3435-3443 (2015).
- Afantitis, A., Tsoumanis, A., Melagraki, G. Enalos Suite of tools: Enhance Cheminformatics
 and Nanoinformatics through KNIME. *Curr Med Chem. DOI:*10.2174/0929867327666200727114410 (2020).
- 897 898

883

887

890

893

1 Nanotechnology and Artificial Intelligence to Enable Sustainable and

2 **Precision Agriculture**

3 Peng Zhang¹*, Zhiling Guo¹, Sami Ullah¹, Georgia Melagraki², Antreas Afantitis² and Iseult Lynch¹

¹School of Geography, Earth and Environmental Sciences, University of Birmingham, Edgbaston,

5 Birmingham B15 2TT, UK

⁶ ²Nanoinformatics Department, Novamechanics Ltd, Nicosia, 1065, Cyprus

7 Correspondance should be addressed to P. Z. *Email: p.zhang.1@bham.ac.uk

8

9 Abstract

10 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 11 12 new approaches and integration of knowledge from diverse fields, such as materials science and 13 informatics. The convergence of precision agriculture, whereby farmers respond in real-time to changes 14 in crop growth, with nanotechnology and artificial intelligence offers exciting opportunities for 15 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 16 impacts on soil microbial communities will allow design of nanoscale agrochemicals that combine 17 18 optimal safety and functionality profiles.

- 19
- 20
- 21
- 22
- 23
- 24

25 Introduction

The Green Revolution, i.e. the 3rd Agricultural Revolution, which occurred between the 1950s and 26 27 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 28 29 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, 30 31 declining soil health and fertility, low use efficiency of agrochemicals due mainly to excessive use of 32 fertilizes and pesticides, shrinking arable land *per capita* and diminishing freshwater availability for irrigation¹. Moreover, climate change, as arising from increasing atmospheric CO₂ concentration 33 leading to rising temperature, is likely to further affect the resilience of agricultural soils and their 34 ability to sustain productivity and ensure food security for an increasing human population². 35 36 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 37 crop nutrition and smart plant sensors^{3, 4, 5}. Using nanotechnology, the delivery of fertilizer⁶ can be 38 39 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 uptake⁷. 40 Nano-enabled agriculture is expected to target pests more efficiently using lower amounts of pesticide⁸ 41 42 thereby avoiding widespread impacts on soil health and biodiversity, and improving soil function and nutrient cycling *via* soil microbiome enhancement (optimization of nitriving/denitrifying bacterial 43 communities). Longer term applications include development of smart "sensor" plants, whereby the 44 plant itself is adapted, using targeted delivery of nanomaterials (NMs), for sensing abiotic stress⁹. As 45 with all new technologies however, the risks must be evaluated in parallel with the benefits, and indeed 46 several NMs have been identified to cause negative changes in soil community structure, e.g. TiO₂ 47 NMs cascading negative effects on denitrification enzyme activity and a deep modification of the 48

bacterial community structure after just 90 days of exposure to a realistic concentration of NPs (1 mg 49 kg⁻¹ dry soil)¹⁰, while studies with Ag NMs, which are well-known for their antimicrobial activity have 50 51 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 NMs¹¹. Thus, an 52 important caveat at the outset of this review is that NMs represent a very broad spectrum of 53 chemistries, compositions and physicochemical properties, which are dynamic and evolving as the 54 55 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. 56

However, as noted in the aforementioned reviews^{3, 4, 5}, the development of nanotechnology for 57 agricultural applications is still at an early stage and is moving forward quite slowly. Significant 58 differences may exist between nanotechnology-based pesticides and conventional pesticides, including 59 altered bioavailability, sensitivity, dosimetry, and pharmacokinetics^{12, 13}. Challenges and barriers 60 include limited understanding of plant-NMs interactions, limited methods for efficient delivery of NMs 61 to plants and soil, risks of potentially hazardous effects of NMs to human health from accumulation of 62 NMs and active ingredient residues in edible portions of plants⁴, and to long term soil quality and soil 63 health from accumulation of NMs and their degradation products in soil and resultant potential 64 alterations in microbial biodiversity¹⁴. There is an urgent need to address these barriers and achieve a 65 66 true win-win scenario, whereby improved agricultural production, reduced environmental pollution 67 from agriculture and lower costs for farmers can be achieved synergistically. A one-health approach to 68 nano-agriculture was proposed by Lombi et al., that requires interdisciplinarity and the bridging of human and environmental health research¹⁵. Computational approaches including artificial intelligence 69 70 (A.I.) and machine learning (M.L.) modelling will undoubtedly play critical roles in the progess of 71 nano-enabled agriculture, and are already starting to gain regulatory acceptance for NMs safety 72 assessment.

| 73 | The application of computers and artificial intelligence (A.I.) in agriculture is not new – for |
|----------------------|---|
| 74 | example, articles addressing software for integrated resource management ¹⁶ , image digitization for soil |
| 75 | and crop science ¹⁶ , and light and temperature monitoring and control for plants ¹⁷ were published 35 |
| 76 | years ago! The rise of remote sensing and integration of remote sensing data into decision support tools |
| 77 | for contemporary farming systems is expected to improve yield production and management while |
| 78 | reducing operating costs and environmental impact ¹⁸ . Agricultural systems models have emerged over |
| 79 | the last 50 years, spanning field, farm, landscape, regional, and global spatial scales and engaging |
| 80 | questions in past, current, and future time periods. Integrated agricultural systems models combining |
| 81 | grasslands and cropping models, livestock models, pest and disease models and risk behaviour models |
| 82 | are also emerging, although data gaps exist across all aspects, hampering their implementation ¹⁹ . |
| 83 | However, the comvergence of A.I. approaches and nano-enabled agriculture is in its infancy and as |
| 84 | such the current perspective aims to stimulate the development of this important area. |
| 85 | The rapid pace of the development of nanotechnologies, the enormous diversity of physico- |
| 86 | chemical properties of NMs and their dynamic interactions with, and transformations, by their |
| 87 | surrroundings (e.g., corona formation, dissolution, sulfidation etc. ^{20, 21}) leads to the need for <i>in silico</i> |
| 88 | approaches to predict and assess their safety ²² . Nanoinformatics is a powerful way of relating the |
| 89 | nanostrucutural features with functional properties based on data-driven A.I. and M.L. approaches ^{22, 23} |
| 90 | ²⁴ . Nanoinformatics emerged a decade ago in the context that development and implementation of |
| 91 | nanotechnology in the real world requires the harnessing of information at the nexus of environmental |
| | |
| 92 | and human safety, risk assessment and management, physiochemical properties and function. With A.I. |
| 92 93 | and human safety, risk assessment and management, physiochemical properties and function. With A.I. and M.L. enabled <i>in silico</i> risk assessment ²⁵ , NMs grouping and classification ²⁶ , and safe-by-design ²⁷ |
| 92 93 94 | and human safety, risk assessment and management, physiochemical properties and function. With A.I. and M.L. enabled <i>in silico</i> 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 |
| 92 93 94 95 | and human safety, risk assessment and management, physiochemical properties and function. With A.I. and M.L. enabled <i>in silico</i> 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 |

not been explored, including for prediction of NMs interactions with and impacts on rhizosphere 97 98 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 99 data are emerging in all these areas^{32, 33, 34}, and a dedicated effort to integrate and curate this data, and 100 101 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 NanoSolveIT³⁵. Coupling these 102 approaches with existing models for nutrient cycling³⁶, NUE³⁷ and crop productivity³⁸ and the 103 aforementioned agricultural systems models into an overall Integrated Approach for Testing and 104 105 Assessment (IATA) will allow co-optimisation of NMs for use in agricultural systems that combine 106 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.

114

115 **Current challenges in agriculture**

With an ever increasing human population under a decreasing per capita agricultural land globally³⁹, 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 121 122 fertilizer use culture thus poses a serious threat to environmental quality as large amounts of nutrients 123 are lost into water and air causing eutrophication and greenhouse effects. For example, agriculture contributes nearly 11% of global greenhouse gas emissions⁴². Nitrogen (N) and phosphorus (P) 124 125 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 environment⁴³. Rockstrom et al. 126 recommended a reduction of reactive N use in agriculture from 150 Mt N y⁻¹ to about 35 Mt N y⁻¹ 127 globally to ensure sustainability⁴³. Such a reduction can only be achieved through a combination of 128 approaches including targeted nano-enabled delivery of fertilizer to match plant demands to avoid 129 130 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 131 fertility of soils, utilize farm yard manure and slurries for meeting nutrient demands and identifying 132 crop breed that are efficient in nutrient uptake and even fixing atmospheric N_2 directly or thorugh 133 enhance symbiosis are some of the key measures to enhance NUE, reduce excessive fertilization and 134 the subsequent losses of reactive N from cultivated soil⁴⁴. Unlike N, available terrestrial P reserves are 135 non-renewable and the current losses of available P from agriculture to water (rivers and oceans) is 10 136 times the pre-industrial and agricultural intensification era⁴³. This unsustainable use of P fertilizer in 137 agriculture is thus posing a risk to global food security⁴⁵, while causing eutrophication of fresh and 138 coastal water bodies, together with N⁴¹. 139

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 achieved⁴⁶. Recent efforts to enhance NUE include utilization of biofertilization to enhance microbial biodiversity⁴⁷, 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 imagery⁴⁸. 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 productivity⁴³.

151 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 152 microbial diseases and pest damage also cause 34% of crop loss ⁴⁹. The application of synthetic 153 154 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 retention⁵⁰; 155 however, these agrochemicals, which are designed to kill, also cause severe adverse impacts on the 156 157 health of human and non-targeted organisms and soil fertility, and result in contamination of water, soil and air⁵¹. Mis-use of agrichemicals on poor quality soils, soil degradation as a result of farming 158 159 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 160 atmospheric CO₂ levels and increasing temperatures also potentially impact the future of agriculture.⁵³ 161

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 168 safety and functionality profiles and implementation of nano-agrichemicals into mainstream
 169 agricultural systems management.

170

171 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.



179

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.

184

185 Increasing crop yields and production rates

186 The Green Revolution relied highly on the traditional agronomic factors including use of synthetic 187 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.

192 One promising way to enhance crop yield is using 'plant nanobionics', a recently coined term 193 referring to the approach of designing NMs to interact with plants in order to enhance native functions or to give the plant non-native functions⁹. A key focus is to improve the efficiency of photosynthesis, 194 195 an essential process occurring in plant leaves which uses solar energy to produce sugar from CO₂ and 196 water for plant growth. Photosynthesis efficiency can be enhanced by improving the efficiency of the 197 photosynthetic enzyme ribulose-1,5-bisphos-phate carboxylase/oxygenase (RuBisCO). A pioneering 198 study found that TiO₂ NMs promote the photosynthesis rate by activating the RuBisCO carboxylation process, potentially the result of the photocatalytic activity of TiO₂ NMs⁵⁴. More recently, root 199 200 application of carbon dots (CDs) was found to enhance RuBisCO activity thus improving the photosynthesis efficiency and carbonhydrate production in Arabidopsis thaliana⁵⁵, leading to 20% 201 202 increase of plant yield; this enhancement of plant growth was also demonstrated for several other plant 203 species such as soybean, tomato and eggplant. The overlapping adsorption of CDs with chloroplasts at 204 $420 \sim 700$ nm and the photo-induced electron donating and accepting properties of CDs are considered 205 to contribute to the enhanced photosynthesis efficiency. Other NMs, such as multiwalled carbon nanotubes (MWCNTs)⁵⁶ and CeO₂ NMs have also shown potential for improving plant phtosynthesis 206 under stress conditions^{57, 58}. CeO₂ NMs can scavenge free radicals such as hydroxyls in mesophyll cells 207 208 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 $400 \sim 700$ nm with energy conversion efficiency less than 4%. Single walled carbon nanotubes (SWCNTs) are capable of

212 capturing a broad range of solar light covering ultraviolet, green and near-infrared. Seminal work by 213 Giraldo et al. found that SWCNTs can insert into the thylakoid membrane, and that the formed 214 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 SWCNTs⁹. Using SWCNTs as a 215 carrier also enabled gene-delivery into chloroplast, a structure that is hard to target using current (often 216 liposome-based) methods⁵⁹, to improve light capture efficiency. The nanotubes also prevented the non-217 218 native DNA from integrating into the plant genome thus avoiding consumer concerns over genetically 219 modified crops. Importantly, the delivery efficiency is plant species independent and may help with 220 high-throughput screening of plants to identify phenotypes with desired functions, e.g., optimised 221 photosynthesis efficiency. For example, it could facilitate the engineering of C3 crops (e.g., rice, wheat) 222 to use the C4 pathway (e.g., maize), which have nearly 50% higher light use efficiency and higher N 223 and water use efficiency than C3 pathway plants.

224

225 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 226 227 resources whilst reducing agricultural derived environmental pollution, which is one of the main pillars 228 of the sustainable vision. Crop yield is highly dependent on external inputs of N, P and potassium (K) 229 and micronutrients (e.g., B, Fe, Mn, Cu, Zn) into the agricultural land. The overall NUE by plants currently stands at less than 50% globaly⁴⁰, with the rest retained in soil, leached into water, or emited 230 231 into air, causing detrimental environmental impacts. Engineered NMs offers great opportunity to 232 improve NUE via nano-based smart delivery platforms, i.e. so-called controlled release and targeted delivery for efficient plant uptake⁶⁰, or through NM influence on microbial communities and their 233 nitrogen fixing abilities⁵⁵. For example, using hydroxyapatite nanoneedles as carriers of urea can 234 235 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 236 the air.⁶ Such a system could also deliver pesticide active ingredients more efficiently thus reducing the 237 238 amount of pesticides needed. For example, nano copper pesticides show four orders higher efficacy against bacterial blight on pomegranate at 10⁴ times lower concentrations than that recommended for 239 copper oxychloride⁶¹. Nanotechnology also allows the nutrients or pesticides to be delivered only at the 240 target position, such as the plant rhizosphere. These strategies reduce the use of fertilizers and 241 242 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 243 agrochemicals, Lowry et al.⁴ also pointed out that selective removal or recovery of nutrients from 244 245 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 246 abundance⁶², thus could potentially be used to intentionally alter the singaling and community structure 247 248 of microbiome (e.g., N fixating bacteria) to enhance the availability of nutrients to plants. It is also 249 possible to increase the population of beneficial symbiotic bacteria (endophyte) to enhance crop 250 productivity; however, as noted by Lowry et al., achieving this requires better understanding of the 251 connection of soil and plant microbiome and the plant physiology involved⁶³. One primising approach to address these knowledge gaps, and facilitate development of initial A.I. models, could be soilless 252 growth systems such as hydroponics⁶⁴, where introduction plant growth-promoting rhizobacteria and 253 use of multi-element sensors and interpretation algorithms based on machine learning logic to monitor 254 255 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 256 257 soil systems.

258

259 Improving management of soil health and plant growth

260 Nanotechnology can also enable smart sensing of undesirable ambient biotic (plant pathogens, weed 261 competition, insect damage) and abiotic (drought or flooding, high salanity, extreme climate) stressors, 262 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 263 been recently reviewed by Giraldo et al⁵. For example, the secretome of microbes, fungi, rhizosphere 264 265 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 266 inventories of secreted proteins under normal, biotic and abiotic stress conditions revealed several 267 268 different types of novel secreted proteins, such as leaderless secretory proteins potentially involved in 269 the defense/stress responses, which could be explored (including computationally, see later sections for details) for use as biomarkers⁶³. Molecule specific NMs-based sensors could be designed to detect 270 271 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, 272 especially if coupled with stimuli-responsive release^{67, 68}. Stimuli responsive sensing systems can 273 274 deliver agrochemicals only when it is necessary in response to environmental changes such as shortage 275 of nutrients, extreme pH conditions, elevated temperature or CO₂. These strategies will greatly improve 276 agronomic management and resilience of agroecosystems to stress, especially under changing climate 277 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 agrochemicals⁶⁸. 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
- 285 benefit trade-offs should be considered in the development of NMs for application in agriculture.
- 286 While in terms of both risk and application of NMs, current studies in the lab, mesocosms and
- 287 field are expensive, time-consuming and complicated, limiting the range of conditions that can be
- 288 varied systematically. Results are often hard to conclude because the interpretation of the results is
- 289 influenced by factors such as experimental procedures, protocols, duration, NMs types, doses, soil
- 290 types and plant species. Integrating of the existing data, albeit with gaps and limitations, and
- 291 supplementation with predictive modelling and machine learning approaches, including Bayesian
- 292 networks^{71, 72}, for example, which can be dynamically updated as new knowledge emerges, into IATA
- 293 offer exciting new directions; development of a nano-agriculture IATA case study utilising the OECD
- 294 IATA case study approach⁷³ 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 nanoenabled agriculture.
- 301

302 A.I. and machine learning for agronomy

303 A.I. and machine learning approaches

304 As computer power increases, and the value of data as knowledge to be exploited is realized more and 305 more, A.I. and machine or deep learning approaches are emerging as means to identify patterns in large 306 datasets that are predicitve of future outcomes. One of the most widely used approaches involves neural 307 networks algorithms, which use an unbiased subset of the total available data as the training set to 308 develop a model that makes predictions using the rest of the data and the validity of the predictions are 309 evaluated to ensure that they could not arise randomly. The size and range of the dataset used to train 310 the model provides the limits to its predictive power, or its domain of applicability – models cannot 311 predict reliably outside their range of data. Box 1 describes the various types of data-driven machine 312 learning models, among which are models that link structure or properties (e.g. of a chemical) to 313 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 314 incorporating uncertainty into decision support systems⁷⁵, by providing a basis for probabilistic 315 316 inference and facilitating assessment of changes in probabilistic belief as new evidence is entered into 317 the model. The larger the dataset available to train a machine learning model, the more powerful it will 318 be - typically in drug discovery or chemoinformatics for example, models will utilize data from 319 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 plants⁷⁶. Box 1. The main types of Machine Learning algorithms, and examples of their application in agriculture and/or nanomaterials design and safety assessment⁷⁷

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 toxicity⁷⁹.

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 imageprocessing 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 data⁸⁰, 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 suspension⁸¹.

Potential applications in nano-enabled agriculture: could be applied to prediction of NMs transformations under different soil and climate conditions; for prediction and clustering of efficacy of nano-enabled agrichemicals 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 environment⁸².

Applications in NMs deisgn, safety and interactions: A recent example used Kohonen networks⁸³, 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 toxicity⁸⁴.

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

<mark>NUE.</mark>

323

324 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 properties⁸⁵. 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 network⁷⁵.

332 In terms of the key areas identified for improvements in crop production, process based machine learning models (e.g., the SPACSYS model⁸⁶) for plant growth, incorporating assimilation, 333 334 respiration, water and N uptake, partitioning of photosynthate and N, N-fixation for legume plants and root growth⁸⁷, are emerging and being constantly improved. With increased understanding of the 335 336 processes, and the availability of intervention strategies such as precision nanoagrochemicals, the 337 potential of machine learning for optimisaiton of agroecosystems has never been higher; integrating 338 machine learning, simulation, and portfolio optimization can inform decisions and support selection of 339 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 quality⁸⁸. Indeed, a 340 341 very recent review of the potential impacts of A.I. on the achievement of the UN sustainable 342 development goals (SDGs) suggested that A.I. will be an enabler for SDG2 on sustainable agriculture, 343 but highlights generally that the pace of development of A.I. may have implications in terms of a lack 344 of regulatory oversight and insight, which could potentially result in gaps in transparency, safety, and ethical standards⁸⁹. 345

346 *Nanoinformatics models applicable to nano-enabled agriculture*

347 The application of machine learning in NM risk assessment, and for design of "safe" and 348 environmentally friendly NMs, is also an area of intensive research in the last few years. For example, 349 nanoQSAR models linking specific NMs properties to uptake by, and impacts on, cells or organisms 350 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 351 internalization⁷⁹), and can be applied for design of targeting strategies in precision nano-agriculture. 352 Similarly, extending advances in nanomedicine to precision nanoagriculture will facilitate the design of 353 optimized controlled release agrochemicals^{90, 91}. For example, deep learning employing an automatic 354 355 data splitting algorithm and the evaluation criteria suitable for pharmaceutical formulation data was developed for the prediction of optimal pharmaceutical formulations and doses⁹². From an agricultural 356 357 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 358 359 parameters. Such data-driven models require significant amounts of data to train and validate them, 360 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. 361 utilizing Electronic Laboratory Notebooks), annotation with relevant ontological terms mapped to the 362 data schema of the receiving databases and automated upload to nanosafety knowledgebases⁹³, which 363 364 in the medium term will facilitate the aggregation, integration and re-use of nanosafety and nano-365 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 agrochemicals⁹⁴. A recent review has assessed the regulation of pesticides for risk assessment and the potential use of *in silico* computerbased chemical modeling technologies to facilitate risk assessment of nano-enabled pesticides⁹². 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.

375

376 Challenges and barriers to precision nano-agriculture

377 Although nanotechnology demonstrates high potential in a wide range of applications in agriculture, it 378 is still primarily at the research stage. There are many challenges to be overcome to move this area 379 forward from basic research to full commercial scale application. This includes lack of mechanistic 380 understanding of the interaction at NM-plant-soil interface and NM uptake and translocation in plant 381 vascular structure and organells; insufficient understanding of the environmental safety and human 382 health risks of intentional NM application; lack of soil and large scale field study to demonstrate the 383 efficacy of NMs under realistic scenarios; and an unclear balance between adoption of a new 384 technology and the low profit margin in agriculture, and the aforementioned challenges regarding 385 collection and harmonization of the datasets needed for development of A.I models.

386 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 387 388 pesticides or fungicide; however, the potential impact on non-target organisms (e.g., beneficial plant 389 rhizosphere bacteria, worms) and long term impacts on soil quality are not known. Although 390 nanofertilizers may enhance the NUE, effects (e.g., alteration of the content of carbonhydrates, macroor micro- nutrient) of NMs on the nutritional quality of food have been reported⁹⁵ and need to be 391 392 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 393

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.

396 NMs undergo numerous transformations (physically, chemically or biologically) in soils and 397 plants. For example, many metal based NMs such as ZnO, Cu and Ag tend to dissolve and release 398 metal ions, which can further react with soil and plant components such as phosphate, sulfur, chloride 399 etc. The original NM properties that are designed for specifc application purpose might not be 400 maintained due to these processes. For example, antifungal NMs such as Ag NMs can be oxidized, 401 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 diminished¹⁰⁰. Some 402 403 transformations might release toxic components, for example, graphene oxide was reported to degrade 404 under sunlight and relase PAH (polycyclic aromatic hydrocarbon) -like compounds which are likely to exhibt toxic properties and persist in the environment¹⁰¹. 405

406 Computational tools that can predict NM transformation processes will favour the design to 407 manipulate or even simulate directly the transformation in order to maintain the NM function or modify 408 their impacts. However, the complexity of soil chemistry and the high responsivity of plants and their 409 secretions into the rhizosphere increase the variability and diversty of potential NM transformations 410 (Figure 3). Many factors are interlinked. For example, NM transformations are affected by the soil and 411 plant microbiome and the excreted extracellular polymeric substances (EPS) and plant root exudates 412 around the rhizosphere. However, plant root exudate composition and microbiome can affect each 413 other and both may be altered due to NM exposure, which can in-turn affect the NM transformation 414 processes. Changes to the microbiome will affect the N cycling processes in soil. Foliar applied NMs 415 can translocated downwards to root and interact with phyllosphere components such as microorganism 416 and leaf exudates. All of the above are also subject to further change and disruption as a result of 417 climate changes, e.g., altered CO₂ and temperatures can shift nutrient cycling, alter rates of reactions /

418 trasnformations, change plant susceptibility to NMs and more. Therefore, the dynamic nature of the 419 whole system needs to be considered making this a perfect candidate for A.I. and machine learning 420 solutions.

Compared to small molecules toxicity prediction, nanoinformaticians are used to working with 421 422 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 423 424 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 425 concentrations in the water, plant mass and emitted to air under controlled temperatures and CO_2 426 427 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 428 applicability of the model, i.e. at least one of the NMs in the training and test set had some overlap with 429 the properties of the "new" NM. If the NMs were characterisered over time under the different 430 conditions, e.g., in terms of their size, dissolution, acquired corona composition, further models 431 432 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) 433 or localization of the NMs in the plants were determined, increasingly complete models of NUE versus 434 435 localsiation in plants could be developed. System complexity can then be build by moving to soils for 436 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 437 fate of NMs in the environment²¹. Thus, the steps will be small initially, but as the datasets and models 438 439 emerge, their integration with other models and tools into overall IATA and agricultural systems 440 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.

448

441

449 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 456 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 457 458 sustainable agriculture. For example, A.I. may predict NM impacts on the agricultural ecosystem and 459 their performance in improving agricultural production (NUE, reduction in air and water pollution 460 forms of key elements), by integrating experimental data from across different soil conditions and 461 different plant species/climate change conditions and NM physicochemical properties, which enables 462 safer-by-design development of nanoagricultural chemicals. Future reseach directions are outlined here 463 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 nanoagriculture 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**.

464 1) Understand the long term fate of NMs in agricultural environment including transport, 465 transformation in soil, and uptake and translocation in plant. Transformation of NMs will change their 466 original designed properties, which may defunctionalize their use as fertilizers, pesticides, carriers, or 467 sensors. The transformation could occur in soil, at plant interface (e.g., root or leaf surface) and inside 468 plant. In soil, the transformation could be driven by soil texture and chemistry, and by interaction with 469 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 470 471 composition at the these regions, including plant metabolites and microorganisms, drive the 472 transformation. NMs may also transform during their translocation in plant vascular structure by 473 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. 488 3) Take a systems level approach to nano-enabled agriculture. The behavior, fate and impact of 489 NMs in soil-plant system, and plant and microorganisms are all interconnected. As shown in Figure 3 490 and described above, change of one factor may induce a change of the whole system. Given the power 491 of A.I., and the complexity of the optimization challenges facing nano-agriculture, it is clear that their 492 convergence offers exciting new directions (Figure 4). Utilising extensive existing models and datasets 493 for soil quality, crop yield and NUE, for example, and combining these with models and datasets 494 related to plant and microbial secretomes, and nanomaterials physicochemical properties, 495 trasnformations and bioavailability, and release of active ingredients, could enable important new 496 insights into (1) the likely transformation pathways for the NMs and their resulting environmental 497 transport and bioavailablity; (2) the potential impact of the NM and their associated active ingredients 498 (in cases where the NMs are carriers) on crop yield and NUE; and (3) potential identification of 499 biomarkers of crop health / diseasae that can be utilized as early warning systems. Identification of data 500 gaps can also drive the design of focused experiments to gap-fill or to develop sub-models to integrate 501 into an overall model framework allowing design of NMs and active ingredient combinations that 502 optimize NUE and minimize pollution whilst enhancing crop yield and potentially even nutritional 503 (calorific) value. Integration of safe-by-design approaches, and feeding forward the emerging 504 knowledge into updating of regulatory process for advanced nano-enabled agricultural applications, 505 both in fertilization and in plant protection is essential also.



507



515

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-filling, and data splitting into tets and validateion sets for modelling¹⁰² (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 523 soil and plant systems and facilitate the design of NMs that can be delivered to plants efficiently. NM 524 transformation in different soil conditions and different root rhizosphere compositions under changing 525 climate conditions, could be also predicted by integrating predictive models which allowing 526 optimization of NMs for agricultural application in a range of climatic and local conditions. Wider 527 ecosystems effects, and prediction of tripartite (NMs-soil-plant) behaviours under future climate 528 scenarios can also be predicted, utilizing for example Baysian networks. Such models are especially 529 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 530 531 sustainable development goal of "improved nutrition and promote sustainable agriculture" (SDG2) will 532 provide important new intersectional insights and suggestions for ways forward.

533

534 Acknowledgements

535 IL, AA and GM acknowledge funding from the EU H2020 projects RiskGone (Grant Agreement N^o 536 814425), NanoSolveIT (Grant Agreement N^o 814572) and NanoCommons (Grant Agreement N^o 537 731032). IL, PZ and ZG acknowledge support from the UoB Institute for Global Innovation 538 Environmental Pollution Solutions theme.

539

540 Author contributions

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

543

544 **Conflict of interests**

545 There are no conflicts of interest to declare.

546

547 **References**

550

553

556

559

562

565

569

572

575

579

- Shahzad, A. N., Qureshi, M. K., Wakeel, A., Misselbrook, T. Crop production in Pakistan and low nitrogen use efficiencies. *Nat. Sustain.* 2, 1106-1114 (2019).
- 551 2. He, W., Yoo, G., Moonis, M., Kim, Y., Chen, X. J. P. Impact assessment of high soil CO₂ on 552 plant growth and soil environment: a greenhouse study. *Peer J.* **7**, e6311 (2019).
- 554 3. Kah, M., Tufenkji, N., White, J. C. Nano-enabled strategies to enhance crop nutrition and 555 protection. *Nat. Nanotechnol.* **14**, 532-540 (2019).
- 4. Lowry, G. V., Avellan, A., Gilbertson, L. M. Opportunities and challenges for nanotechnology in the agri-tech revolution. *Nat. Nanotechnol.* **14**, 517-522 (2019).
- 560 5. Giraldo, J. P., Wu, H., Newkirk, G. M., Kruss, S. Nanobiotechnology approaches for 561 engineering smart plant sensors. *Nat. Nanotechnol.* **14**, 541-553 (2019).
- 563 6. Kottegoda, N., *et al.* Urea-hydroxyapatite nanohybrids for slow release of nitrogen. *ACS Nano*564 **11**, 1214-1221 (2017).
- Kabiri, S., Degryse, F., Tran, D. N., da Silva, R. C., McLaughlin, M. J., Losic, D. Graphene
 oxide: A new carrier for slow release of plant micronutrients. ACS Appl. Mat. Interfaces 9, 43325-43335 (2017).
- 570 8. Huang, B., *et al.* Advances in targeted pesticides with environmentally responsive controlled
 571 release by nanotechnology. *Nanomaterials* 8, 102 (2018).
- 573 9. Giraldo, J. P., *et al.* Plant nanobionics approach to augment photosynthesis and biochemical sensing. *Nat. Mat.* **13**, 400-408 (2014).
- Simonin, M., Richaume, A., Guyonnet, J. P., Dubost, A., Martins, J. M., Pommier, T. J.
 Titanium dioxide nanoparticles strongly impact soil microbial function by affecting archaeal nitrifiers. *Sci. Reports* 6, 1-10 (2016).
- 580 11. Grün, A.-L., *et al.* Impact of silver nanoparticles (AgNP) on soil microbial community
 581 depending on functionalization, concentration, exposure time, and soil texture. *Environ. Sci.*582 *Eur.* 31, 15 (2019).
- Stone, D., Harper, B. J., Lynch, I., Dawson, K., Harper, S. L. Exposure assessment:
 recommendations for nanotechnology-based pesticides. *Int. J. Occup. Environ. Health* 16, 467474 (2010).
- 588 13. Kookana, R. S., *et al.* Nanopesticides: guiding principles for regulatory evaluation of
 environmental risks. *J Agric Food Chem* 62, 4227-4240 (2014).
- 14. Richarz, A.-N., Lamon, L., Asturiol, D., Worth, A. P. J. Pitfalls. Perspectives. Current developments and recommendations in computational nanotoxicology in view of regulatory applications. Computational Nanotoxicology, Chapter 2, 99-155 (2019).

595 15. Lombi, E., Donner, E., Dusinska, M., Wickson, F. J. A One Health approach to managing the 596 applications and implications of nanotechnologies in agriculture. Nat. Nanotechnol. 14, 523-531 597 (2019). 598 599 16. Heermann, D. F., Duke, H. R., Buchleiter, G. W. 'User friendly'software for an integrated 600 water-energy management system for center pivot irrigation. Comput. Electron. Agric. 1, 41-57 601 (1985). 602 603 17. White, J. W., Hamilton, J. H. Irradiance and plant temperature monitor/controller. Comput. 604 *Electron. Agric.* 1, 95-103 (1985). 605 606 18. Chlingaryan, A., Sukkarieh, S., Whelan, B. Machine learning approaches for crop yield 607 prediction and nitrogen status estimation in precision agriculture: A review. Comput. Electron. 608 Agric. 151, 61-69 (2018). 609 610 19. Jones, J. W., et al. Toward a new generation of agricultural system data, models, and 611 knowledge products: State of agricultural systems science. Agri. Systems 155, 269-288 (2017). 612 613 Xu, L., Xu, M., Wang, R., Yin, Y., Lynch, I., Liu, S. The Crucial Role of Environmental 20. 614 Coronas in Determining the Biological Effects of Engineered Nanomaterials. Small 16, 615 2003691 (2020). 616 617 Svendsen, C., et al. Key principles and operational practices for improved nanotechnology 21. environmental exposure assessment. Nat. Nanotechnol. 15, 1-12 (2020). 618 619 620 22. Winkler, D. A. J. S. Role of Artificial Intelligence and Machine Learning in Nanosafety. Small 621 **16**, 2001883 (2020). 622 623 Burello, E., Worth, A. A theoretical framework for predicting the oxidative stress potential of 23. 624 oxide nanoparticles. Nanotoxicology 5, 228-235 (2011). 625 626 24. Karatzas, P., et al. Development of deep learning models for predicting the effects of exposure to engineered nanomaterials on Daphnia Magna. Small 16, 2001080 (2020). 627 628 629 25. Cohen, Y., Rallo, R., Liu, R., Liu, H. H. In silico analysis of nanomaterials hazard and risk. 630 Acc. Chem. Res. 46, 802-812 (2013). 631 632 26. Lamon, L., et al. Grouping of nanomaterials to read-across hazard endpoints: from data 633 collection to assessment of the grouping hypothesis by application of chemoinformatic 634 techniques. Part. Fibre Toxicol. 15, 37 (2018). 635 636 27. Varsou, D.-D., et al. A safe-by-design tool for functionalised nanomaterials through the Enalos 637 Nanoinformatics Cloud platform. Nanoscale Adv. 1, 706-718 (2019). 638 639 28. Findlay, M. R., Freitas, D. N., Mobed-Miremadi, M., Wheeler, K. Machine learning provides 640 predictive analysis into silver nanoparticle protein corona formation from physicochemical properties. Environ. Sci.: Nano 5, 64-71 (2018). 641

643 29. Duan, Y., *et al.* Prediction of protein corona on nanomaterials by machine learning using novel descriptors. *NanoImpact* 17, 100207 (2020).

642

645

649

653

657

661

664

668

671

675

679

683

- Ban, Z., Yuan, P., Yu, F., Peng, T., Zhou, Q., Hu, X. Machine learning predicts the functional composition of the protein corona and the cellular recognition of nanoparticles. *Proc. Natl. Acad. Sci.* 117, 10492-10499 (2020).
- Afantitis, A., Melagraki, G., Tsoumanis, A., Valsami-Jones, E., Lynch, I. nanoinformatics
 decision support tool for the virtual screening of gold nanoparticle cellular association using
 protein corona fingerprints. *Nanotoxicology* 12, 1148-1165 (2018).
- McManus, P., *et al.* Rhizosphere interactions between copper oxide nanoparticles and wheat
 root exudates in a sand matrix: Influences on copper bioavailability and uptake. *Environ. Toxicol. Chem.* 37, 2619-2632 (2018).
- 33. Zhang, P., Guo, Z., Zhang, Z., Fu, H., White, J. C., Lynch, I. Nanomaterial Transformation in the Soil–Plant System: Implications for Food Safety and Application in Agriculture. *Small* 16, 2000705 (2020).
- 662 34. Zhang, P., *et al.* Plant species-dependent transformation and translocation of ceria nanoparticles. *Environ. Sci.: Nano* **6**, 60-67 (2019).
- Afantitis, A., *et al.* NanoSolveIT Project: Driving nanoinformatics research to develop innovative and integrated tools for in silico nanosafety assessment. *Comput. Struct. Biotechnol. J.* 18, 583-602 (2020).
- 669 36. De Willigen, P., Neeteson, J. Comparison of six simulation models for the nitrogen cycle in the soil. *Fertilizer Res.* 8, 157-171 (1985).
- 672 37. Pathak, H., *et al.* Modelling the quantitative evaluation of soil nutrient supply, nutrient use
 673 efficiency, and fertilizer requirements of wheat in India. *Nutr. Cycling in Agroecosyst.* 65, 105674 113 (2003).
- Janssen, B. H. Simple models and concepts as tools for the study of sustained soil productivity
 in long-term experiments. II. Crop nutrient equivalents, balanced supplies of available nutrients,
 and NPK triangles. *Plant Soil* **339**, 17-33 (2011).
- Klein Goldewijk, K., Dekker, S. C., van Zanden, J. L. Per-capita estimations of long-term
 historical land use and the consequences for global change research. *J. Land Use Sci.* 12, 313337 (2017).
- Lassaletta, L., Billen, G., Grizzetti, B., Anglade, J., Garnier, J. 50 year trends in nitrogen use
 efficiency of world cropping systems: the relationship between yield and nitrogen input to
 cropland. *Environ. Res. Lett.* 9, 105011 (2014).
- 41. van Grinsven, H. J., Bouwman, L., Cassman, K. G., van Es, H. M., McCrackin, M. L., Beusen,
 A. H. Losses of ammonia and nitrate from agriculture and their effect on nitrogen recovery in

| 690 691 692 | | the European Union and the United States between 1900 and 2050. J. Environ. Qual. 44, 356-367 (2015). |
|--|------------|---|
| 693 694 695 | 42. | Burney, J. A., Davis, S. J., Lobell, D. B. Greenhouse gas mitigation by agricultural intensification. <i>Proc. Natl. Acad. Sci.</i> 107 , 12052-12057 (2010). |
| 696 697 698 | 43. | Rockström, J., et al. Planetary boundaries: exploring the safe operating space for humanity. Ecol. Soc. 14, (2009). |
| 699 700 701 | 44. | Raza, S., <i>et al.</i> Piling up reactive nitrogen and declining nitrogen use efficiency in Pakistan: a challenge not challenged (1961–2013). <i>Environ. Res. Lett.</i> 13 , 034012 (2018). |
| 702 703 704 | 45. | Cordell, D., Drangert, JO., White, S. The story of phosphorus: global food security and food for thought. <i>Global Environ. Change</i> 19 , 292-305 (2009). |
| 705 706 707 708 | 46. | Van Grinsven, H. J., Erisman, J. W., de Vries, W., Westhoek, H. Potential of extensification of European agriculture for a more sustainable food system, focusing on nitrogen. <i>Environ. Res. Lett.</i> 10 , 025002 (2015). |
| 709 710 711 | 47. | Schütz, L., <i>et al.</i> Improving crop yield and nutrient use efficiency via biofertilization—A global meta-analysis. <i>Front. Plant Sci.</i> 8 , 2204 (2018). |
| 712 713 714 | 48. | Sharma, L. K., Bali, S. K. A review of methods to improve nitrogen use efficiency in agriculture. <i>Sustainability</i> 10 , 51 (2018). |
| 715 716 | 49. | Oerke, EC. Crop losses to pests. J. Agri. Sci. 144, 31-43 (2006). |
| 717 718 719 720 | 50. | Bindraban, P. S., Dimkpa, C., Nagarajan, L., Roy, A., Rabbinge, R. Revisiting fertilisers and fertilisation strategies for improved nutrient uptake by plants. <i>Bio. Fertil. Soils</i> 51 , 897-911 (2015). |
| 721 722 723 | 51. | Aktar, W., Sengupta, D., Chowdhury, A. Impact of pesticides use in agriculture: their benefits and hazards. <i>Interdiscip. Toxicol.</i> 2 , 1-12 (2009). |
| 724 725 726 | 52. | National Academies of Sciences, E., Medicine. Science breakthroughs to advance food and agricultural research by 2030. National Academies Press (2019). |
| 720 727 728 | 53. | Parry, M. L. Climate change and world agriculture. Routledge (2019). |
| 720 | | |
| 729 730 731 | 54. | Gao, F., <i>et al.</i> Mechanism of nano-anatase TiO 2 on promoting photosynthetic carbon reaction of spinach. <i>Biol. Trace Elem. Res.</i> 111 , 239-253 (2006). |
| 729 730 731 732 733 734 | 54. 55. | Gao, F., <i>et al.</i> Mechanism of nano-anatase TiO 2 on promoting photosynthetic carbon reaction of spinach. <i>Biol. Trace Elem. Res.</i> 111, 239-253 (2006). Li, H., <i>et al.</i> Enhanced RuBisCO activity and promoted dicotyledons growth with degradable carbon dots. <i>Nano Res.</i> 12, 1585-1593 (2019). |

738 739 57. Wu, H., Shabala, L., Shabala, S., Giraldo, J. P. J. E. S. N. Hydroxyl radical scavenging by 740 cerium oxide nanoparticles improves Arabidopsis salinity tolerance by enhancing leaf 741 mesophyll potassium retention. Environ. Sci.: Nano 5, 1567-1583 (2018). 742 743 58. Wang, Y., et al. Alleviation of nitrogen stress in rice (Oryza sativa) by ceria nanoparticles. 744 Environ. Sci.: Nano https://doi.org/10.1039/D0EN00757A (2020). 745 746 59. Kwak, S.-Y., et al. Chloroplast-selective gene delivery and expression in planta using chitosan-747 complexed single-walled carbon nanotube carriers. Nat. Nanotechnol. 14, 447-455 (2019). 748 749 60. Guo, H., White, J. C., Wang, Z., Xing, B. Nano-enabled fertilizers to control the release and use 750 efficiency of nutrients. Curr. Opin. Environ. Sci. Health 6, 77-83 (2018). 751 752 61. Mondal, K. K., Mani, C. Investigation of the antibacterial properties of nanocopper against 753 Xanthomonas axonopodis py, punicae, the incitant of pomegranate bacterial blight. Ann. 754 Microbiol. 62, 889-893 (2012). 755 756 Asadishad, B., Chahal, S., Cianciarelli, V., Zhou, K., Tufenkji, N. Effect of gold nanoparticles 62. 757 on extracellular nutrient-cycling enzyme activity and bacterial community in soil slurries: role 758 of nanoparticle size and surface coating. Environ. Sci.: Nano 4, 907-918 (2017). 759 760 63. Agrawal, G. K., Jwa, N. S., Lebrun, M. H., Job, D., Rakwal, R. Plant secretome: unlocking 761 secrets of the secreted proteins. Proteomics 10, 799-827 (2010). 762 763 64. Sambo, P., et al. Hydroponic solutions for soilless production systems: Issues and opportunities 764 in a smart agriculture perspective. Front. Plant Sci. 10, 923 (2019). 765 766 65. Jung, D. H., Kim, H.-J., Choi, G. L., Ahn, T.-I., Son, J.-E., Sudduth, K. A. Automated lettuce 767 nutrient solution management using an array of ion-selective electrodes. T. ASABE 58, 1309-768 1319 (2015). 769 770 66. Girard, V., Dieryckx, C., Job, C., Job, D. Secretomes: the fungal strike force. Proteomics 13, 771 597-608 (2013). 772 773 Camara, M. C., Campos, E. V. R., Monteiro, R. A., Santo Pereira, A. d. E., de Freitas Proença, 67. 774 P. L., Fraceto, L. F. Development of stimuli-responsive nano-based pesticides: emerging 775 opportunities for agriculture. J. Nanobiotechnol. 17, 100 (2019). 776 777 68. Xu, X., Bai, B., Wang, H., Suo, Y. A near-infrared and temperature-responsive pesticide release 778 platform through core-shell polydopamine@ PNIPAm nanocomposites. ACS Appl. 779 Mat.Interfaces 9, 6424-6432 (2017). 780 781 Tian, H., Kah, M., Kariman, K. Are nanoparticles a threat to mycorrhizal and rhizobial 69. 782 symbioses? A critical review. Front. Microbiol. 10, 1660 (2019). 783 784 70. Eymard-Vernain, E., et al. Impact of a model soil microorganism and of its secretome on the 785 fate of silver nanoparticles. Environ. Sci. Technol. 52, 71-78 (2018).

- 787 71. Murphy, F., *et al.* A tractable method for measuring nanomaterial risk using Bayesian networks.
 788 *Nanoscale Res. Lett.* 11, 503 (2016).
 789
- Furxhi, I., Murphy, F., Poland, C. A., Sheehan, B., Mullins, M., Mantecca, P. Application of
 Bayesian networks in determining nanoparticle-induced cellular outcomes using
 transcriptomics. *Nanotoxicology* 13, 827-848 (2019).
- 794 73. OECD Environment Health and Safety Publications Series on Testing and Assessment No. 46.
 (2004).
 796
- 74. Kar, S., Roy, K., Leszczynski, J. On applications of QSARs in food and agricultural sciences:
 history and critical review of recent developments. In: *Advances in QSAR Modeling*. Springer
 (2017).
- Tari, F. A Bayesian network for predicting yield response of winter wheat to fungicide
 programmes. *Comput. Electron. Agric.* 15, 111-121 (1996).
- Krouk, G., Lingeman, J., Colon, A. M., Coruzzi, G., Shasha, D. Gene regulatory networks in plants: learning causality from time and perturbation. *Genome Biol.* 14, 123 (2013).
- 807 77. Baştanlar, Y., Özuysal, M. Introduction to machine learning. In: *miRNomics: MicroRNA* 808 *Biology and Computational Analysis*. Springer (2014).
 809
- 810 78. Nemes, A., Rawls, W. J., Pachepsky, Y. A. Use of the nonparametric nearest neighbor approach
 811 to estimate soil hydraulic properties. *Soil Sci. Soc. Am. J.* **70**, 327-336 (2006).
- Afantitis, A., Melagraki, G., Tsoumanis, A., Valsami-Jones, E., Lynch, I. A nanoinformatics
 decision support tool for the virtual screening of gold nanoparticle cellular association using
 protein corona fingerprints. *Nanotoxicology* 12, 1148-1165 (2018).
- 80. Pedroso, M., Taylor, J., Tisseyre, B., Charnomordic, B., Guillaume, S. A segmentation algorithm for the delineation of agricultural management zones. *Comput. Electron. Agric.* 70, 199-208 (2010).
- 81. Bi, X., et al. Quantitative resolution of nanoparticle sizes using single particle inductively
 coupled plasma mass spectrometry with the K-means clustering algorithm. J. Anal. At.
 Spectrom. 29, 1630-1639 (2014).
- 825 82. Bu, F., Wang, X. A smart agriculture IoT system based on deep reinforcement learning. *Future*826 *Gener. Comput. Syst.* 99, 500-507 (2019).
- 828 83. Sun, B., Barnard, A. S. Visualising multi-dimensional structure/property relationships with 829 machine learning. *J. Phys.: Mat.* **2**, 034003 (2019).
- 84. Lamon, L., Aschberger, K., Asturiol, D., Richarz, A., Worth, A. Grouping of nanomaterials to read-across hazard endpoints: a review. *Nanotoxicology* 13, 100-118 (2019).
- 833

786

793

800

806

812

816

820

824

827

- 834 85. Liakos, K. G., Busato, P., Moshou, D., Pearson, S., Bochtis, D. Machine learning in agriculture:
 835 A review. *Sensors* 18, 2674 (2018).
- 837 86. Liang, S., Zhang, X., Sun, N., Li, Y., Xu, M., Wu, L. Modeling crop yield and nitrogen use
 838 efficiency in wheat and maize production systems under future climate change. *Nutr. Cycling*839 *Agroecosyst.* 115, 117-136 (2019).
- 841 87. Liu, Y., *et al.* Modelling field scale spatial variation in water run-off, soil moisture, N2O
 842 emissions and herbage biomass of a grazed pasture using the SPACSYS model. *Geoderma* 315, 49-58 (2018).
- 845
 88. Sundaramoorthi, D., Dong, L. Machine-Learning-Based Simulation for Estimating Parameters in Portfolio Optimization: Empirical Application to Soybean Variety Selection. *Available at SSRN 3412648*, https://dx.doi.org/10.2139/ssrn.3412648 (2019).
- 849 89. Vinuesa, R., *et al.* The role of artificial intelligence in achieving the Sustainable Development Goals. *Nat. Commun.* 11, 1-10 (2020).
 851
- 852 90. Kaddi, C. D., Phan, J. H., Wang, M. D. Computational nanomedicine: modeling of 853 nanoparticle-mediated hyperthermal cancer therapy. *Nanomedicine* **8**, 1323-1333 (2013).
- 855 91. Kumar, P., Khan, R. A., Choonara, Y. E., Pillay, V. A prospective overview of the essential requirements in molecular modeling for nanomedicine design. *Future Med. Chem.* 5, 929-946 (2013).
- Yang, Y., Ye, Z., Su, Y., Zhao, Q., Li, X., Ouyang, D. Deep learning for in vitro prediction of pharmaceutical formulations. *Acta Pharm. Sin. B* 9, 177-185 (2019).
- Martinez, D. S. T., Da Silva, G. H., de Medeiros, A. M. Z., Khan, L. U., Papadiamantis, A. G.,
 Lynch, I. Effect of the Albumin Corona on the Toxicity of Combined Graphene Oxide and
 Cadmium to Daphnia magna and Integration of the Datasets into the NanoCommons
 Knowledge Base. *Nanomaterials* 10, 1936 (2020).
- 867 94. Hardy, A., *et al.* Guidance on risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain: Part 1, human and animal health. *EFSA J.* 16, (2018).
- 871 95. Zhao, L., *et al.* CeO2 and ZnO nanoparticles change the nutritional qualities of cucumber
 872 (Cucumis sativus). *J Agric. Food Chem.* 62, 2752-2759 (2014).
- Wang, Q., Ma, X., Zhang, W., Pei, H., Chen, Y. The impact of cerium oxide nanoparticles on tomato (Solanum lycopersicum L.) and its implications for food safety. *Metallomics* 4, 1105-1112 (2012).
- 878 97. Tan, W., *et al.* Effects of the exposure of TiO₂ nanoparticles on basil (Ocimum basilicum) for two generations. *Sci. Total Environ.* 636, 240-248 (2018).
- 880

836

840

844

848

854

858

866

870
- 881 98. Hu, X., Kang, J., Lu, K., Zhou, R., Mu, L., Zhou, Q. Graphene oxide amplifies the phytotoxicity of arsenic in wheat. *Sci. Rep.* 4, 1-10 (2014).
- Be La Torre-Roche, R., *et al.* Multiwalled carbon nanotubes and C60 fullerenes differentially
 impact the accumulation of weathered pesticides in four agricultural plants. *Environ. Sci. Technol.* 47, 12539-12547 (2013).
- Reinsch, B., *et al.* Sulfidation of silver nanoparticles decreases Escherichia coli growth
 inhibition. *Environ. Sci. Technol.* 46, 6992-7000 (2012).
- Hou, W.-C., *et al.* Photochemical transformation of graphene oxide in sunlight. *Environ. Sci. Technol.* 49, 3435-3443 (2015).
- Afantitis, A., Tsoumanis, A., Melagraki, G. Enalos Suite of tools: Enhance Cheminformatics
 and Nanoinformatics through KNIME. *Curr Med Chem. DOI:*10.2174/0929867327666200727114410 (2020).
- 897 898

883

887

890

893

36