How can *ab initio* simulations address risks in nanotech?

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Discussions of the potential risks and hazards associated with nanomaterials and nanoparticles tend to focus on the need for further experiments. However, theoretical and computational nanoscientists could also contribute by making their calculations more relevant to research into this area.

Significant numbers of consumer products based on nanotechnology are entering the market, and large quantities of nanoparticles are now being produced annually. In producing these products, we are confronted with the vexatious reality that the very same physical features that provide the sensitivity and reactivity that are essential for many of these applications may also be a disadvantage when we consider the possible risks and hazards associated with these products[1,2]. Therefore, in parallel with the development of new nanotechnologies, the toxicology of nanomaterials is also under scrutiny[3–5], as is their impact on the environment[6–8] and issues related to workplace safety[9]. This article highlights areas in which *ab initio* computer simulations can help develop our understanding of these hazards, and suggests ways in which existing techniques can be made more applicable to this field of research.

At present, attention is focused on the interaction of nanomaterials with living organisms[10]. It has already been shown that some nanomaterials have the potential to damage skin, brain and lung tissue, and accumulate in the body[10], though consensus on some areas is still lacking. Reports on the toxicity of carbon nanotubes, for example, are delivering both good and bad news. An *in vitro* study measuring the impact of single-walled carbon nanotubes on mitochondria in human A549 lung cells found what appeared to be signs of cytotoxicity in approximately 50% of the cells when MTT (a salt that is not soluble in water) was used, but there were no signs of cytotoxicity when WST-1 (a salt that is soluble in water), was used. Moreover, no cytotoxicity was observed when the salt INT, the dye TMRE or the antibody Annexin-V was used[11]. (All these salts, dyes and antibodies are routinely used in cell viability and proliferation assays). However, exposure of the mesothelial lining of the body cavity in mice to long multiwalled carbon nanotubes has recently been shown to result in asbestos-like, length-dependent, pathogenic behaviour[12]. It has been found that the functionalization of carbon nanotubes can reduce toxicity[13], but stable chemisorption on nanotubes is intrinsically linked to the environmental factors such as pressure and temperature[14].

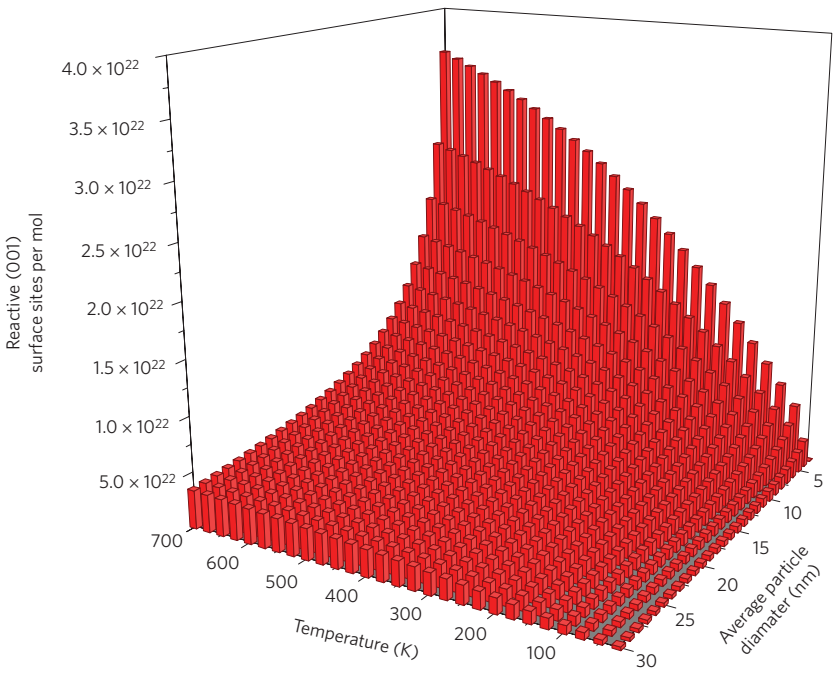

Figure 1 | Density functional theory can be used to predict the fraction of (001) surface facets on polyhedral anatase (a form of titania) nanoparticles as a function of temperature and nanoparticle size. Complementary DFT calculations can also predict the reactivity of these (001) surfaces making it possible to calculate the number of potentially reactive sites per mole of anatase in water[26].

Numerous reports are available that summarize current knowledge and highlight areas requiring more focused attention[15–21], but most of the strategies suggested in these reports are based on inherently experimental approaches to the problem. Not surprisingly, discussions about risks can seem esoteric to theoretical and computational nanoscientists, and somewhat removed from their sphere of influence. However, we are still under scrutiny from our governments, companies, institutions, other nanoscientists, the wider scientific community and society as a whole, and the issue of the potential risks associated with nanotechnology cannot be avoided. So we are confronted with the

inevitable question — what can *ab initio* modellers do to help?

The right tool for the job

Clearly we should start by focusing on the critical areas requiring the most immediate attention. We already know from experiments that the undesirable properties of nanomaterials depend on, and are moderated by, a wide range of physical parameters[15–20] such as size, shape, chemical composition or degree of agglomeration. We also know that many of these dependencies are intrinsically linked[2], and we must take this knowledge into account before we make predictions about possible risks.

Fortunately this is an area where computational nanoscientists have an advantage because, unlike our experimental colleagues, we can control each of these critical parameters independently, and identify underlying mechanisms responsible for instabilities. It is also possible to investigate nanostructures in highly non-equilibrium environments — such as extreme temperatures and pressures, or strong electric or magnetic fields — that cannot be probed experimentally. Using a systematic approach and accurate *ab initio* simulations it is possible to rapidly sample parameter space, and build much needed predictive capabilities with a high degree of confidence.

Recent examples of such work include the characterization of the surface reactivity of ferrihydrite nanoparticles assembled in ferritin (an iron storage protein) using molecular orbital/density functional theory (MO/DFT) calculations[22]; the characterization of the surface reactivity of gold nanoparticles using extended Hückel theory combined with DFT calculations[23]; and a DFT study of the nanotoxicological implications of oxygen adsorption at silver surfaces (including *ab initio* molecular dynamics)[24]. Among the computational methods used in materials physics, DFT (a quantum mechanical theory principally used to investigate the electronic structure) offers the greatest sensitivity to chemical reactions and is an extremely powerful method for calculating the ground-state properties of metals, semiconductors and insulators.

Another pertinent example is titanium dioxide. This mineral, also known as titania, occurs in three forms: rutile, anatase and brookite. Concern has focused on nanoparticles of the anatase form because photocatalytic activity on the surface of these nanoparticles can produce reactive oxygen species[1], which can be damaging to health. The (001) surface of the anatase form has been shown to be particularly reactive[25], though the relative fraction of this surface that is found in samples depends on the temperature and chemical environment[26]. However, DFT can be used to predict the number of reactive sites on the surface of polyhedral particles, as a function of temperature and nanoparticle size (Fig. 1).

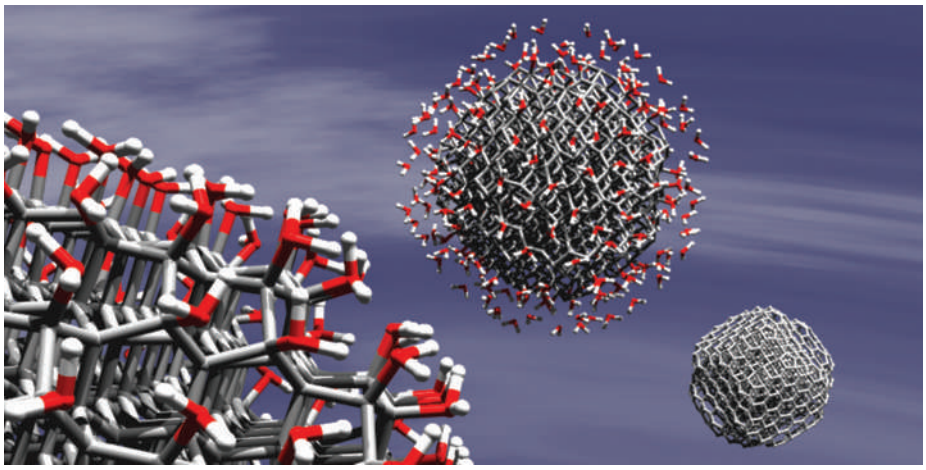

Figure 2 | Real nanoparticles interact with the gases, liquids and other nanoparticles surrounding them. These chemical and physical interactions can be included computer simulations to give insights into the structure and stability of nanoparticles in natural environments.

Although theory and simulation have a lot to offer, especially in the area of bio–nano interactions[1] — such as the recent computer simulations showing fullerene translocation through lipid membranes[27] — very few of us are funded to study these issues. However, when conducting the research that we are funded to do, there are a few computational and theoretical accommodations we can make that will allow our existing work to be more useful to those who are focused on nanohazards, as the following three examples illustrate.

The problem with zero temperature

To put it rather bluntly, the problem with zero temperature is that nothing actually takes place. Certainly the highly accurate *ab initio* calculations that can only be performed at zero temperature have allowed us to calculate details of electronic structure that could not be calculated any other way. Moreover, the information gained from such simulations about the structure of nanomaterials has improved our understanding of morphological stability and reactivity. However, it is clear that a nanoparticle inside our bodies, in contact with our skin or released into an ecosystem will not be at zero temperature.

One way that temperature effects may be included in *ab initio* simulations is to include the entropic contribution to the Gibbs free energy, as opposed to simply using the potential energy, as described by the second law of thermodynamics. There are various robust methods for calculating the free energies, beginning with traditional methodologies based on harmonic approximations, thermodynamic integration and lambda integration methods, complemented by more specialized approaches (see ref. 28 for a review).

Finite temperatures may also be included in computational studies by using *ab initio* versions of well-known classical methods such as molecular dynamics (for example, *ab initio* molecular dynamics or Car–Parrinello molecular dynamics) or Monte Carlo simulations to obtain the equilibrium geometry (at temperatures greater than zero), rather than optimization methods such as conjugate gradient or steepest decent approaches (which are temperature independent). A significant proportion of computational studies are performed to determine the low-energy (equilibrium) geometry of the system under consideration, and use this equilibrium geometry to model representative physical properties or interactions with other systems. If these geometries are obtained using molecular dynamics or Monte Carlo simulations at finite temperature, the results will be more relevant to real nanomaterials under realistic conditions.

Treating the full range of temperatures that may be experienced by nanomaterials throughout their life-cycle may be unrealistic for some of us, but in the first instance, it will certainly help if we adopt

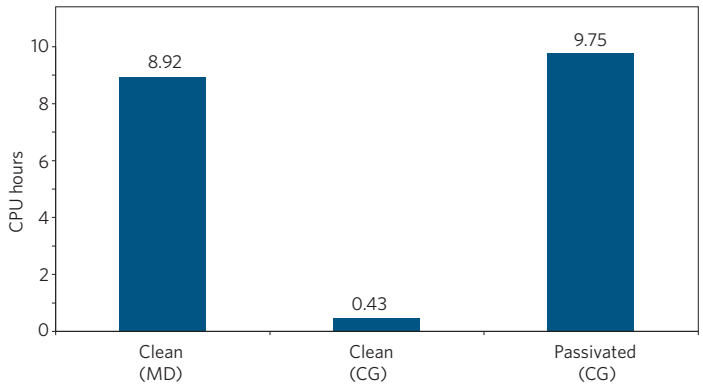

Figure 3 | Number of CPU hours needed to simulate a periodic 64 atom [100] oriented slab of platinum using three approaches: molecular dynamics (MD) at 300 K, conjugate gradient methods (CG), and a fully hydrogen passivated version of the same slab using CG. Although using a finite temperature or passivation increases the CPU time by a factor of about 20, the results are more relevant to the real world. CPU hours were calculated with VASP using DFT-PBE and PAW pseudopotentials on the Australian National Computational Infrastructure SGI Altix 3700 Bx2 cluster with 1928 1.6 GHz Itanium2 processors. The MD approach was equilibrated after 140 fs, based on analysis of thermodynamic properties and root-mean-square deviation of atomic positions.

room temperature (rather than zero temperature) as a new standard.

Simulating the right environment

This brings us to the relationship between the stability of nanomaterials and their chemical environment. Although a large number of nanostructures are produced under ultrahigh-vacuum conditions, very few of them are stored or intended for extended use under these conditions, and most will eventually be exposed to air and/or water (at least). This may seem unimportant but we are starting to appreciate that, just as nanoparticles can affect the environment, environmental changes (such as exposure to air or water) can also have an effect on nanomaterials. It has been shown, for example, that 3-nm zinc sulphide nanoparticles synthesized in methanol show a reversible structural transformation associated with methanol desorption, and subsequent binding of water to the nanoparticle surface, at room temperature[29].

As nanomaterials have a high surface area, maintaining stable surfaces both in devices and in storage media is of critical importance, and computer simulations are ideal for exploring the structure of surfaces and identifying even the smallest change in the position of atoms near edges, corners, surface steps and defects. Most reports in the literature involve conveniently 'clean' surfaces that are experimentally unrealistic (other than in ultrahigh-vacuum conditions). To make our calculations realistic we therefore need to passivate the surfaces of the nanostructures we are simulating by, for example, adding monolayers of small molecules. Depending on the chemical environment in question, this could mean chemisorption or physisorption (Fig. 2). Irrespective of the specific interaction, there is a considerable (and reliable) body of literature examining the adsorption of molecules on surfaces to guide the placement and configuration of these adsorbates, and more advanced solvation methodologies integrated into some software packages. Hence, it is suggested that our new default standard should be to passivate our structures with the most ubiquitous environmental components: water or the main reactive constituents of air.

Isolation and agglomeration

As mentioned above, common concerns raised in various reports[15–20] distinguish between isolated nanomaterials and those already integrated into products and devices. Individual nanoparticles are a source of concern, as studies have shown that they are capable of passing through cell membranes, moving through the body by means of the circulatory system, and potentially passing through the blood–brain barrier[21]. This forms the basis of many biomedical applications such as drug delivery and medical imaging, and illustrates that a detailed understanding of the properties of individual nanoparticles is imperative.

This is another area that can be tackled by *ab initio* simulation with relative ease, as we are used to looking at single, isolated nanostructures. However, in real specimens, nanoparticles tend to agglomerate and form larger superstructures that are easily perturbed by environmental factors such as changes in temperature, pressure and pH. Therefore, in addition to understanding the properties of individual nanoparticles, there is also a need to understand the interactions between nanoparticles. The precise nature of interparticle interactions, the structure of the interface, and the packing of arrays and superstructures can be difficult to probe experimentally, and again this represents another an opportunity for computational nanoscientists.

As one would expect, the best strategy is to include more than one nanoparticle in our simulations[30]. However, simulations with many nanoparticles can make individual calculations too computationally intensive and impractical for DFT. There is a simple way that we can address this issue without devoting additional resources or conducting supplementary simulations that are beyond the scope of our investigations. When examining the structure of free surfaces it is often customary to use a three-dimensional periodic supercell containing a two-dimensional 'slab' of material to represent a facet; it is also common to use three-dimensional supercells in simulations of one-dimensional structures. When performing these simulations we take great care to ensure that the structures are isolated from their mirror images by adding sufficient vacuum space to obtain convergence of, for example, binding energies, dipole interactions and charge distributions. But as we search for the ideal separation distance (to balance the computational load and the accuracy of the results) we are also gathering valuable information about the interactions between the surfaces of the structure and its surroundings. A more detailed analysis of this (existing) data could assist in understanding what drives agglomeration and self-assembly, and is worthy of inclusion in our publications.

Conclusions

So, can *ab initio* simulations help address potential hazards and risks in nanoscience and nanotechnology? The answer is a resounding yes. As our models become more sophisticated, and computational resources more accessible, we are well placed to engage these new challenges[28,31,32]. Although we are often more focused on other aspects of nanoscience and nanotechnology, we are studying the right materials and we have developed the right methods. There are, however, few ways that we can make our calculations more accessible to those

working specifically on nanohazards, as outlined here. I am not advocating that we place these accommodations ahead of our mandated research — only that we should consider them when it does not conflict with our existing objectives (Fig. 3), and of course, I include myself in this vision.

Sometimes, computer simulation is the right tool for the job, as shown by the increase in support for computational studies examining the interaction of nanoparticles with biological systems. Given the more specific, quantitative knowledge gained from theory and simulation we can build predictive models that will facilitate the design of more appropriate storage systems, protect nanomaterials from the environment as much as they protect the environment (and us) from them, and allow us to construct algorithms for assessing the likelihood of toxicity in a variety of natural environments. ❐

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