1
An Introduction to Nanochemistry Concepts

1.1
Nanochemistry – What's in a Name?

Despite its name and history, nanochemistry should not be defined only in terms of a length scale; such a definition would miss much of the conceptual novelty and diversity of nanochemistry. An educational way to "define" this field is instead through those concepts, ideas, and tools that, taken together, distinguish nanoscience from the rest of chemistry and physics. The goal of this chapter is to introduce those concepts.

The approach we adopted to introduce you to this subject is multidisciplinary; the concepts presented should be amenable to teachers and students from chemical and physical, materials science and engineering, and biological and medical disciplines. A physicist, for example, will be able to teach the principles and practice of nanochemistry to a group of physics students using the road map we delineate, but using the language of physics. Nanoscience students from other disciplines in such a class will all benefit from the more analytical physics approach to nanomaterials, peppered with just the right amount of nanochemistry detail; the same can be said about teachers from the other science, engineering and biological backgrounds.

This educational philosophy should be appealing to teachers from any discipline whose goal is to get across the basics of nanochemistry in a way that is tailored to both teacher and students. It is an experiment in teaching and learning the rudiments of nanoscience and nanotechnology through the chemistry of nanomaterials, where the "nano" food chain begins, and in which we are all guinea pigs.

education: training; strengthening and developing powers of the mind through instruction

The challenge of teaching nanochemistry lies in its diversity. Its topics and objectives often seem unrelated. Discovering its intimate connections is much like traveling to the home of an ancient culture, where every town has its own traditions, habits, foods, and dialects. It takes years even to get a glimpse of the spirit of a nation.

connected: interrelated or associated; linked

This learning curve can be eased by giving you the tools with which to divide a nanochemistry problem into its simplest com-

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ponents. These tools are few, and intimately but subtly connected. In this book you will see these connections and thus hopefully the solutions, the possibilities, and the marvelous diversity this field encompasses.

The price to pay for this shortcut is that the tools are rather conceptual in nature. You will not find details here. You will not find mathematical proofs either. You will find instead a concentrate of ideas, some a little philosophical, and many unlike anything you are used to from a scientific textbook. We have done our best to ease your way through, but only so much help can be effective.

1.2
On the Surface of Things

Scientists like approximations. They like shortcuts to gain rapid insight into a puzzle or to solve a problem quickly. Of the common approximations in solid-state physics and chemistry, one of the most famous is the absence of interfaces. By interface we mean that volume in space, often approximated as a surface, which separates much larger volumes of dissimilar substances, such as two different solids, a solid and a liquid, and so on.

approximations: inexact results whose precision is considered adequate

Mathematics, the language of science, dislikes sharp transitions, so interfaces are synonymous with havoc for scientists. Surfaces are thus often considered as perturbations in an otherwise homogeneous system or even ignored altogether [1]. These approaches are usually adequate with bulk materials since surfaces represent only a minimal fraction of their volume.

With the advent of nanotechnology and the miniaturization of materials to the nanometer scale the surface becomes impossible to ignore, as demonstrated in Figure 1.1, which shows how the surface-to-volume ratio of a spherical nanocrystal increases with decreasing diameter. For a PbS structure, a diameter of ~5 nm is small enough for the majority of the atoms to lie on the surface.

While you might now see its relevance, you might still wonder what a surface looks like. If we imagine each atom as a box it would look like the example in Figure 1.2.

dangling bonds: these bonds occur at a surface when atoms have unfilled outer orbital (valence) shells

Atoms at the surface usually possess dangling bonds, as depicted in Figure 1.2 by the orange cylinders. Such bonds are unsaturated (unsatisfied), they often bear a partial electric charge, and they increase the energy of the surface, and of the whole material, by an amount equal to:

$$\gamma = n_{\mathrm{db}} \frac{\Phi}{2}$$

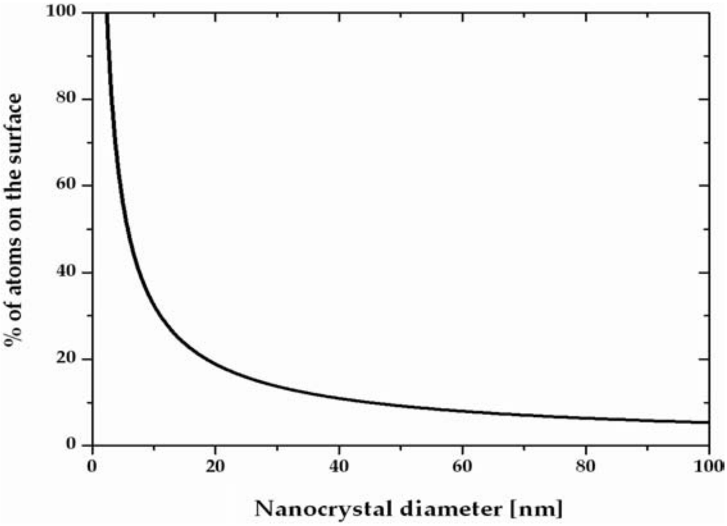

Figure 1.1 This graph shows the approximate percentage of surface atoms as a function of nanocrystal size, assuming a spherical morphology and a PbS lattice.

where γ is the surface energy, n_{db} is the surface density of dangling bonds, and Φ is the energy of the bond. What we learn from this formula is that the surface energy increases with the density of dangling bonds, which is determined by the composition of the surface, and also by its roughness and curvature. This powerful formula also tells us that different crystal faces, which expose different densities or types of atoms, will have different amounts and kinds of dangling bonds, and thus different surface energies. You will see later how this fact is used to grow nanocrystals with the most diverse shapes, and how those shapes and crystal facets influence the chemical and physical properties of the crystals, their function, and their ultimate usefulness in nanotechnology.

Now, what is surface energy? In practice one has to keep in mind that Nature likes to reduce the free energy. This means that it will try to reduce the surface energy by causing those dangling bonds to react, while a chemist might instead want to use them as substrates for a surface reaction. The surface energy thus determines how a surface interacts with the environment; a surface with higher energy is more reactive as it is more prone to reduce its own energy by interacting with the environment. Impurities, for example, are readily adsorbed on the surface and often segregated there because they can compensate dangling bonds and thus reduce the surface energy (see Figure 1.3). This fact alone has phenomenal repercussions in solid-state synthesis and impacts greatly in fields like catalysis, fuel cells, batteries, and

substrate: in chemistry this terms is generally used to indicate a reagent on which a chemical reaction occurs; in materials science it generally indicates a solid surface on which some material is deposited; in this book both meanings will be used, depending on the context

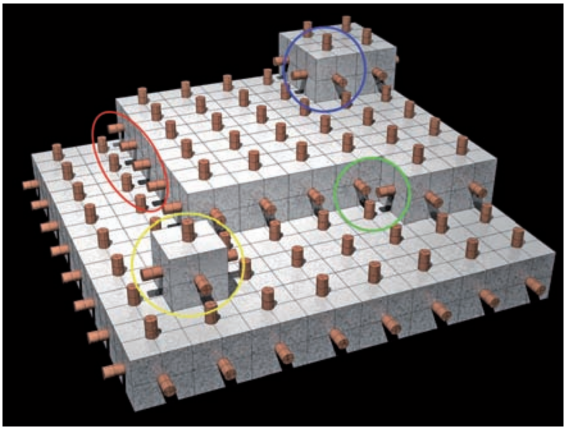

Figure 1.2 Here is shown a representation of a surface as it is often found in atomistic crystal growth models. Each 4 × 4 cube represents an atom and each rod represents a dangling bond or unsaturated (unsatisfied) valence, in other words an orbital that protrudes into space and which can be empty or contains a single or pair of valence electrons. You can clearly see that where surface corrugation occurs (corners, kinks, and edges) the density of dangling bonds increases. Different kinds of corrugations (highlighted with the colored ellipses) also generate different densities of dangling bonds and have different stabilities. The atom highlighted in yellow, for example, is very labile as it is bound to the crystal with only one bond while the one highlighted in blue is more stable, being triply bound to the surface. The density of dangling bonds not only determines the surface energy but also the local electron density and reactivity. This is the reason why crystal growth and many chemical and catalytic reactions preferentially happens at high-energy sites like the edges (red ellipse) or kinks (green ellipse).

Figure 1.3 Here is depicted a hollow nanocrystal (or a cross-section of a nanotube if you prefer), with the important surface effects one can expect in nanoscale systems, as described in the text. From the top you can see surface functionalization, where molecules or functional groups are grafted through surface chemistry to the surface dangling bonds; the grafting reduces the surface charge and relieves the pressure generated by the surface energy which is indicated by the arrows. There can be defects in the surface modification, often related to edges or kinks that leave the surface locally more reactive. Just below the surface functionalization you can see the phenomenon of faceting, when the surface energy is reduced by creating atomically flat surfaces which thus possess fewer dangling bonds. On the left is shown the effect of the adsorption of impurities that can satisfy the dangling bonds and the surface charges, thereby decreasing the surface energy and thus the pressure. On the bottom left you can see how surface charges can be used in the deposition of monolayers or multilayers of charged species like polyelectrolytes. On the bottom right is shown a pictorial representation of surface reconstruction, when dangling bonds partially recombine and the atoms reposition themselves in order to reduce the surface energy. On the right is shown how a nanoscale convex surface will have significantly increased solubility when compared to the bulk material, while in the center of the void is shown how the opposite is true for a nanoscale concave surface. In the centre of the void is also shown how concave surfaces can be functionalized with molecules, and that cavities can be used to entrap guests.

chemical sensing, where high surface reactivity and selectivity are paramount.

You might wonder if nano, by creating so many surfaces, is not really "swimming upstream", fighting against Nature. In fact, this picture is partly accurate. However, you will learn in this book the extraordinary techniques that allow us to control and temper the surface energy through clever surface-specific chemical reactions, making our swimming a bit easier.

Besides the adsorption of impurities, the higher energy of the surface is often partly compensated by a process called surface reconstruction (see Figure 1.3). The positions and bonding of the atoms at the surface are generally a bit different from those in the bulk. In addition, atoms at

impurities: in chemistry impurities are generally moieties of molecular or atomic nature which are where they do not belong

segregation: in materials science this terms indicates when a particular structure or moiety within a mixture unmixes, generating sizable and independent islands with different properties and/or composition

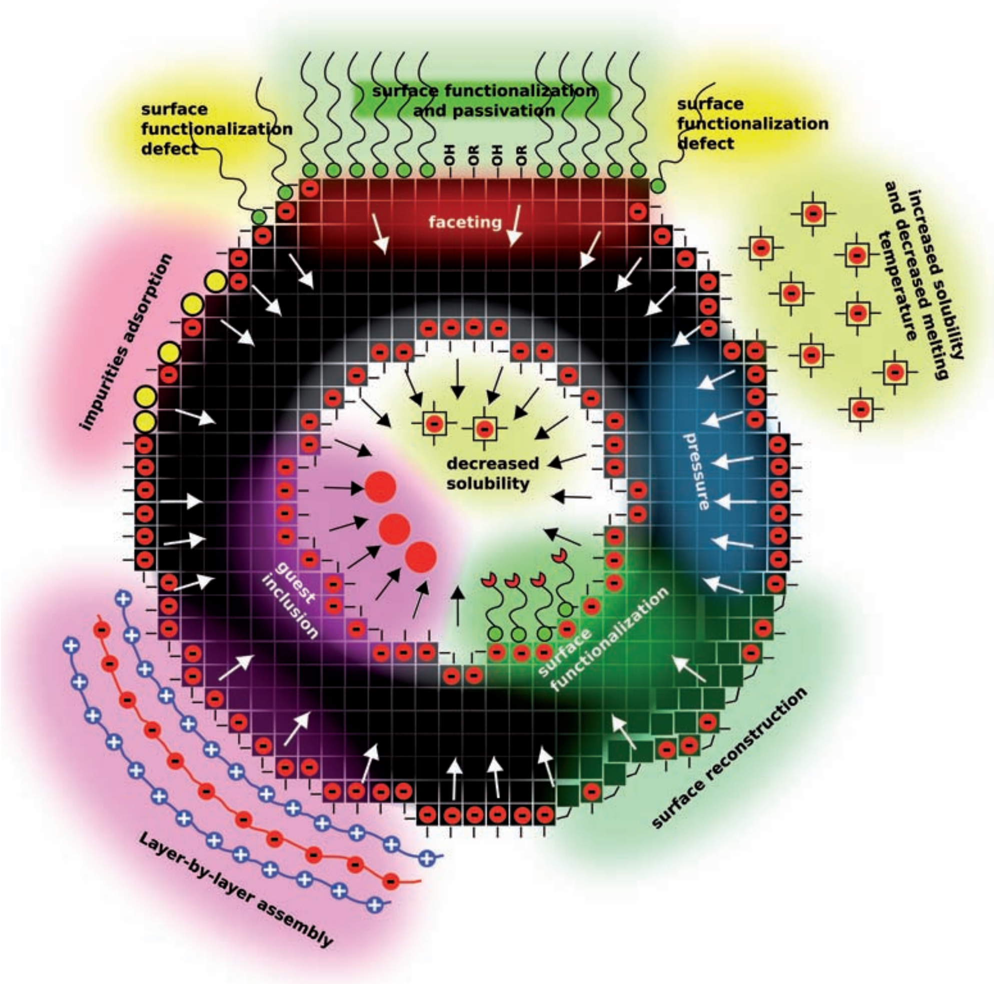

Figure 1.3 (caption see p. 14)

the surface are pushed by an external pressure, expressed by the Laplace law, and whose direction depends on the surface curvature.

$$\Delta P = 2\frac{\gamma}{r} \text{ (for a spherical surface)}$$

The sign Δ means "difference of…", and where P stands for pressure, r stands for particle radius, and γ is the surface energy (usually of the order of 1 J/m^2). For a radius of 2 nm, the pressure differential at the surface would amount to as much as 1 GPa [2]. This is a huge pressure, which can squeeze the atomic structure several atomic layers down from the surface, or even change it outright (see Figure 1.3). A classic case is a bulk tetragonal ferroelectric perovskite like $BaTiO_3$: at the nanoscale it undergoes surface reconstruction to the paraelectric cubic phase to create a gradient of properties from the outside to the inside of the material. You can imagine that if overlooked, this phenomenon could cause the nanomaterials designer working towards nanoferroelectrics some heartache. Another case is the surface segregation found in alloy nanomaterials where the component with the lowest surface free energy makes its way to the surface, thereby changing a solid solution (a statistical mixture of atomic or molecular components) into a phase-separated core–corona nanomaterial (one component in the bulk and the other component on the surface), equally troublesome if not recognized.

This pressure, strain, and concentration of energy at the surface can be partly relieved by melting, or via surface functionalization which eliminates dangling bonds (see Figure 1.3) [3]. Molecules of different kinds can be grafted, depending on the surface chemistry. One usually can think of surface grafting as a molecule–molecule reaction, in which one of the "molecules" is a dangling bond or a functional group at the surface. For example (please note that R is any organic functional group):

$-OH$ (*exposed group, hydrophilic, typical for oxide surfaces*) + CH_3OSiR_3 (*a sol–gel precursor*) $\rightleftharpoons -OSiR_3$ (*anchored molecule, hydrophobic*) + CH_3OH (*methanol*)

The result of this reaction, for example, is to turn the surface from hydrophilic to hydrophobic, meaning that it will start behaving like your Teflon®-coated pan at home.[1] You can now imagine having sensing molecules, luminescent molecules, or molecules with any desired properties attached to a surface; this is indeed how many devices are synthesized nowadays in leading-edge nano labs around the world.

- *chemical selectivity: this term is used to measure the ability of a substrate to react specifically with one target moiety or with one specific class of moieties*
- *Laplace law: a mathematical relation between the surface pressure of a sphere and its radius and surface energy*
- *surface pressure: this is the pressure that is generated on a surface by its surface energy and it increases with increasing surface curvature*
- *perovskite: this is a class of solid-state structures of general formula ABC_3 where A and B are metallic elements, and C is generally oxygen or one of the chalcogenides (S, Se, Te)*
- *paraelectric: paraelectricity and ferroelectricity are properties that define the way the electric dipoles in a material react upon exposure to an electric field; electric dipoles in paraelectrics do not form oriented domains and thus they orient under a field, strengthening it and returning to the random state upon removal of the field; in ferroelectrics in contrast the dipoles are organized in domains*

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[1] Hydrophobicity and superhydrophobicity are very hot topics as they are the base for technologies like microfluidics where fluids are manipulated in microchannels, allowing calculations to be performed with liquids instead of electrons.

Why, in fact, would you need to use an often expensive pure material with a certain surface property when you can often get the same result by coating an ordinary material with the appropriate molecules?

This ease of surface functionalization comes at a price: surfaces differ from the bulk in that they are not static. They develop, change, and respond to the environment. Dangling bonds or surface groups often react over time with molecules in the atmosphere yielding a "passivation" layer, a term that implies protection of the underlying material. The tarnishing of your silver cutlery in the presence of sulfide contaminants to form a dark film of silver sulfide, which you polish hard with a chemical cleaner to remove, is an example of passivation. So is the tough silicon oxide coating that forms spontaneously on clean silicon from its reaction with oxygen. Such a passivating layer changes the properties of the surface and makes it less reactive (see Figure 1.3).

While it is true that passivation and grafting are very efficient strategies, surface functionalization does not need to form bonds of a covalent or coordinative nature. In most cases, surfaces have a charge which results from the dangling bonds or by the protonation or deprotonation of surface groups: hydroxyls can be deprotonated and become anionic, or amines can be protonated and become cationic. Such charges can be controlled, quantitatively measured, and used in a multitude of ways. First of all, a negatively charged surface can be coated by positively charged molecules, clusters, or polymers using electrostatic (coulombic) attraction. This process can be repeated by depositing alternately charged species on the surface, giving rise to fascinating multilayers. This methodology for building functional nanostructures layer-by-layer and with nanometer precision you will learn more about later (see Figure 1.3, and the chapter on Cadmium Selenide) [4].

Now, where does nano really show its power in the surface game? Due to their size, nanoscopic materials possess huge surface areas, usually in the $\sim$100–1000 m^2/g range – that's right – that large [5]! This means that any phenomenon in which the surface performs an extensive function will take advantage of the increased surface area; think about sensing or catalysis at the nanoscale, or any diffusion-controlled reaction between two nanoscale solids, for example. Coating a mere gram of nanomaterials is equivalent to coating a surface equal to your average apartment with the equivalent bulk material: this is obviously a great asset in trying to detect molecules with high sensitivity, greatly accelerate a chemical reaction, or quickly and efficiently drive solid-state reactions to completion!

But effects get deeper. In fact, while in bulk materials surface functionalization, grafting, and adsorption only affect the properties of the surface, in nanomaterials they also affect the properties of the bulk. So, a silicon nanowire's electrical conductivity can be affected by the adsorption of molecules on its surface; for example you can make

made of iso-oriented (similarly oriented) dipoles – application of an electric field orients the domain but its removal does not bring them back to the random state, thus yielding a remnant polarization in the material

- *tetragonal: "tetragonal" and "cubic" as we refer to them here are related to the symmetry of the atomic structure of the material; a crystal with a specified composition can have different atomic lattice symmetries in different conditions and such different structures are the so called "phases" of the material*
- *ferroelectrics: see "paraelectrics"*
- *cubic: see "tetragonal"*
- *alloy: a homogeneous mixture of metallic elements*
- *solid solution: a statistical mixture of atomic or molecular components*
- *phase separation: see "segregation"*
- *core–corona: a particle whose interior composition and/or phase is different from the outer composition and/or phase*

the smallest pH meter or light switch, or detect pathogens or viruses this way [6].

Another counterintuitive aspect of nanomaterials is that nanomaterials' surfaces behave very differently depending on their curvature, whether the surface is concave or convex. This is a universal phenomenon, but nanostructures, due to their diminutive size, are inherently endowed with such high surface curvatures that such effects are much more pronounced. As you can see in Figure 1.3, one of the main effects is that concave surfaces are less soluble than convex surfaces. We can try to explain this intuitively. Look at the hollow nanocrystal in Figure 1.3; now remove one layer of squares from the entire outer surface. What you are doing is dissolving the material, and what you have achieved is a significant decrease of surface area; you would thus expect this phenomenon to be energetically relatively favored. Now take away a layer of squares only from the flat part of the outer surface. Did you decrease the surface area in this case? Not really, right? So you do not expect this occurrence to be relatively favorable or unfavorable. Ok, now remove a layer of squares from the interior surface, making the hole bigger. What did you get? A higher surface area! This is relatively unfavorable, compared to the other two cases, and thus the solubility will be lower. This partially explains the phenomenon of modified solubility of highly curved surfaces and introduces the concept of concave nanoscale surfaces and, by extension, hollow nanostructures and nanoporous materials.

While you might be more used to think of nanochemistry as a science of nanosolids, it is just as importantly a science of nanovoids, which can be zero-dimensional (a hollow nanocrystal for example), one-dimensional (nanotubes or some mesoporous materials), two-dimensional (a layered system), or three-dimensional (colloidal crystals). You will learn in the following chapters the amazing things chemists have achieved by using pores. But for now, let your imagination loose for a moment! You could envision hollow nanocapsules that can deliver a drug and release it on command, or you could functionalize pores to turn your material into a sensor or a hydrogen-storage material, or you could stuff the pores with a material of choice and then remove the porous mold to leave the nanosized replica...the list goes on. Labs around the world are already working on such ideas but, as you can see, there is no shortage of possibilities with nanovoids; they are not as empty as you may think!

The influence of surface properties does not stop here; they not only affect the underlying nanoscale solid but also the way it interacts with its environment and with others of its kind. Such interactions can be tuned in order to obtain self-assembly [7], which can be briefly defined here as a spontaneous or directed assembly of building blocks into architectures possessing a function.

- *surface functionalization: changing the properties of a surface by changing its chemical composition, usually by adding or substituting a chemical moiety*
- *strain: in materials science it indicates a deformation of the atomic lattice of a crystal usually due to pressure, defects, or electronic effects; it is also used to indicate a deformation in a molecular structure*
- *grafting: a chemical term used to indicate the chemical attachment (usually by covalent bonds) of a molecular moiety to a solid substrate or a polymer chain*
- *melting: undergoing a phase transition from solid to liquid; in nanomaterials it happens at much lower temperatures because of the lower coordination number of surface atoms and lower overall cohesive energy, compared to bulk materials*
- *hydrophilic: water-loving; characterized by strongly polar functional groups*
- *hydrophobic: water-fearing; characterized by non-polar functional groups*

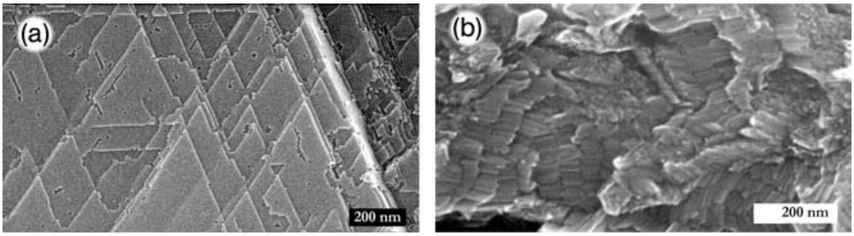

Figure 1.4 Examples of nanocrystal self-assembly mediated by their surface properties; scanning electron microscope images of (a) superlattice of PbS nanocrystals [11]; (b) pseudo-liquid-crystalline arrangement of Bi_2S_3 nanorods [10].

Surface charges, for example, and the resulting attraction or repulsion, can be used to self-assemble magnificently complex nanostructures composed of nanocrystals [8, 9] (see Figures 1.4 and 1.7). In a similar way, van der Waals interactions between surface-anchored molecules on nanorods can be used to self-assemble the nanorods in pseudo-liquid-crystalline arrangements with anisotropic properties [see Figure 1.4, panel (b)] [10]. The relation between the ordering of rod-shaped molecules in a liquid crystal and the alignment of nanorods is fascinating and important with wide-ranging nanotechnological implications which we will reserve for a later discussion.

Surfaces define a great part of the virtues and challenges of nanochemistry; it is thus important to always remember that between you and your favorite nanomaterial there is its surface to be contended with!

passivation layer: this is formed by the reaction of a surface with its environment that renders it more stable

surface charge: the average electronic charge at the surface of a material

protonation: the process of chemical addition of a H^+ ion to a molecule, a surface group, or an atom within a atomic lattice; this process adds a positive charge to its substrate

deprotonation: the process of detachment of a H^+ ion from a molecule, a surface group, or an atom within a atomic lattice; this process removes a positive charge from its substrate

extensive property or function: a material property or function which is proportional to the material's volume, e.g., weight

1.3
Size is Everything. . .Almost

When all approaches to a problem seem to fail, start asking "why?" Our mind limits the range of our thoughts to make us quicker in taking decisions; it does so by using assumptions, that is, notions we assume to be true without a definitive proof. But science is not about believing; it is about moving towards the truth. This is where a scientist has to fight the natural instinct to uncritically accept assumptions. Such a tendency is natural and rather addictive: assumptions reassure us, they keep us warm and fuzzy, they protect us from our uncomfortable ignorance. But in hiding our ignorance, they prevent us from addressing it. This is why you should remember that your creativity as a scientist will not be determined so much by how much you work (even though it helps), but by your imagination, your knowledge, and your ability to temporarily forget what you think you know. This can be summarized in a famous quote attributed to Albert Einstein, which goes something like:

intensive property or function: a material property or function which is not dependent on the material's volume, e.g., density

bulk materials: materials that are large enough that surface and size effects are negligible for most properties and applications; not nano!

solubility: the maximum amount of one substance that can dissolve in another

pores: voids or hollow areas within a "solid" structure

anisotropy: being dependent on spatial direction

isotropy: being independent of spatial direction

liquid crystals: discovered by Reinitzer and von Lehmann in the 1880s, the liquid crystal is a state of matter with behavior intermediate between that of an isotropic liquid and a crystal with long-range translational periodicity; the nematic phase is one of the possible structures liquid crystals can adopt

self-assembly: spontaneous or directed union of building blocks into architectures possessing a function

"Everybody knows what cannot be done, till someone naïve who doesn't know it arrives and does it."

You will see throughout this book how nanochemistry can be a fantastic training ground for you to learn how to go beyond assumptions, as it is mostly based on their breakdown at the nanoscale. What we know as valid assumptions for bulk materials or molecules are often outright false at the nanoscale. We are talking about the intermediate regime between matter and molecules, the fuzzy interface between them, and between the disciplines that have traditionally dealt with them.

As the name says, nanochemistry is also about size, about the length scale spanning 10^{-9} to 10^{-12} m. But, "what is so special about that length scale?" you might ask. Well, back in the early days scientists realized that many meso-phenomena were seen to occur in that size range. Meso means "in the middle" and by meso-phenomena we mean those effects that manifest between the bulk (classical) and molecular (quantum) realms. Things get "weird" in this intermediate regime; they scale with size, and display a strange mix of classical and quantum behavior – a new world of possibilities. Quantum mechanics is known to be counterintuitive. How weird would a material be whose macroscopic behavior is dominated by quantum mechanics. . .? We will see examples of that.

But how "big" is nano? And how "small"? Big and small are among those words which do not belong to scientific discourse. Scientifically speaking, we should say that the nanoscale goes between 1 and 1000 nanometers, approximately between 10 and 10 000 atoms. If a meter were as long as the circumference of the earth, a nanometer would be approximately as long as your thumb (see Figure 1.5). But still you should not think of nano as something small; as a scientist you must learn that nothing is "big" or "small" as size is always relative to something else: a nanocrystal is huge for a molecule but tiny for a human cell, and an individual nanowire cannot be seen by eye, but a massive parallel assembly of them could span a square centimeter! You will see in the following pages that words like "small" or "big" lose meaning in nanoscience as what are truly important are instead the size relations. Einstein stated that time is relative. . .well, size is too.

Relations of size determine size-dependent effects. Some crucial parameters in the description of many properties are measured with lengths, which we can define as characteristic (see Figure 1.5 for some examples).

We can then say that most meso-phenomena emerge when the characteristic length of the property becomes comparable with a characteristic length of the object showing it, or being affected by it. For example, excited electrons in solids leave their "parent" atom but they keep roaming around it at a certain distance which is called the

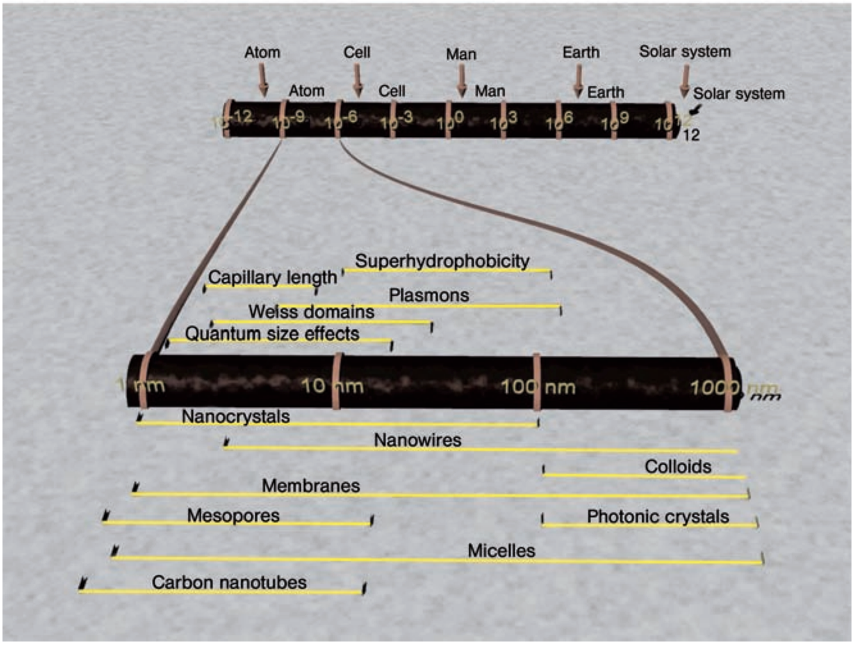

Figure 1.5 Diagram of size relations on a logarythmic scale: The top bar represents the length scales from 10^{-12} to 10^{12} m. The bottom bar is a blowup of the nanoscale regime. On top of the bottom bar are indicated the length scales of some properties, while below the bottom bar are some examples of the available nanomaterials and their typical sizes.

"exciton Bohr radius", which ranges roughly between 2 and 20 nm, depending on the material. When the physical size of the material becomes comparable or smaller than this distance, these electrons start behaving differently and this affects the whole electronic structure, and electrical and optical properties of semiconductors, as we will see later [12].

You will also see that ferromagnetism (permanent magnetism) is characterized by "Weiss domains" within which the magnetic dipoles associated with unpaired electron spin are oriented in the same direction. The size of these domains is also in the nanoscale (usually around 10–50 nm); when you make ferromagnetic materials of that size or smaller, the magnetic order of the material changes dramatically, becoming the so-called giant paramagnetism or "superparamagnetism". Ferroelectric materials, which are basically the analog of ferromagnetic materials for electric fields (they possess a remnant electric field after having been polarized), follow similar rules.

We can thus summarize the previous paragraphs by saying that the workings of the properties in the bulk derive from the fact that

assumption: something taken for granted or accepted as true without proof; a supposition

meso-phenomenon: a phenomenon that manifests between the bulk (classical) and molecular (quantum) regimes and where the length of a characteristic property is comparable with the object's size *exciton: an entity consisting of an electron which has been excited so much as to leave its own atom and the positive charge that it has left behind (called "hole"); these two, being oppositely charged, attract each other forming a large hydrogen-like system; it is in fact so similar to the hydrogen system that it possesses energy levels, a Bohr radius (the exciton Bohr radius), and orbitals that are labelled just as in the hydrogen atom; the main difference is that excitons have a finite lifetime (between* 10^{-9} *and* 10^{-6} *s) and by recombining they produce heat or light*

ferromagnetism: the magnetic analog to ferroelectricity; see the Iron Oxide chapter

superparamagnetism: a magnetic ordering phase in which the material is constituted by a single Weiss domain; the whole material can thus orient its magnetic dipole with the applied magnetic field and this leads to the absence of remanent magnetic field and to very large maximum magnetizations

bulk materials are much larger than the characteristic lengths of those properties. Nanoscience happens when this is not true anymore.

We can translate this dichotomy into more familiar terms if we imagine our material as a canvas on which the property is painted, and the "length scale" of this property is represented by the size of the brush stroke. If the canvas is much larger than the brush stroke you will not see the brush stroke and you will have a Leonardo. But if your canvas is comparable in size with the brush stroke, you will have a completely different painting whose appearance is directly affected by the properties and shape of the stroke, like in a van Gogh. In other words, if bulk materials are Leonardo's, then nanomaterials are van Gogh's.

You can think of size when it comes to nano as follows: when you are thinking of a property or a phenomenon, you should be able to identify a length which is characteristic for it. You will often find that length to lie in the nanoscale, and thus that property or phenomenon will be transformed in a nanomaterial.

Size effects are more interesting than that; they are not an "on–off" kind of thing. They are smoothly size-dependent. Every size below that cutoff is a different nanomaterial with properties defined by scaling laws. What does this mean? Take gold for example: when reduced to the nanoscale, it changes from the metallic gold sheen we know so well, to gold with different colors for every incremental reduction in its size. This phenomenon has been used since the forth and fifth centuries BC in Egypt and China to make colored ceramics but its full understanding has come only recently, starting with Faraday, 150 years ago [13]. Why is this so exciting? Well, it means that whereas before we only knew of a single kind of gold in bulk form, with its associated chemical and physical properties, now we have an entire palette of gold chemistries and properties, an infinity of new gold nanomaterials where every size stands different. You can now imagine the gigantic opportunities for tailoring the function and utility of an infinite library of such gold nanomaterials. While changing the color of a material might sound silly, especially in light of what the media promise from nanotechnology, this simple finding is the basis of a completely new generation of cancer treatments and biomolecule detection platforms that are being tested as we write.

One of the revolutions of nanotechnology lies here: in the possibility, given by nanochemistry, to shrink all the materials we know below the length scales of their properties. We can essentially "reconstruct the periodic table of bulk materials" that we know into an infinity of nanomaterials that we do not know, having the same composition but distinct properties and functions, thereby offering a myriad of opportunities for creating nanotechnologies of a new kind.

1.4
Shape

In nanoscience there are always (at least) two ways to "see" a concept or a problem: from the outside in and from the inside out. The first takes the nanoscale problem and imagines it at a macroscopic length scale; nanocrystals packing into microchannels can be "seen" as golf balls packing into holes; nanowire meshes can be "seen" as spider webs; hexagonal close-packed arrays of nanochannels resemble honeycomb in a beehive.

This approach allows you to draw conclusions based on your sensory experience with the macroscopic world, without getting lost in the crowd of unfamiliar microscopic details. It allows you to visualize a problem or a phenomenon in your mind by putting yourself inside it; it removes the length-scale barrier which makes intuition harder. If you think of a nanorod as if it were just a meter-long rod, it is then usually easier to try and predict how it is going to behave.

While you will be surprised by how "macroscopically" many nanoscopic materials behave, this methodology is clearly insufficient for a real understanding of a nanoscience problem. However, it is an extremely valuable guide on how to model a phenomenon in your mind, without getting overwhelmed by complexity. Once you can "see" a model of the process in your mind you can more easily develop a hypothesis. The whole research process then acquires an internal logic because you have a hypothesis to test, conclusions to verify, and control experiments to perform.

Details can cause your whole initial model to change. The path towards truth becomes a series of jumps from one approximation to another, prodded by the failures of a series of hypotheses. But this is the beauty and the challenge of research, and this is why you must maintain flexibility and must not become attached to your initial "understanding" of things (unfortunately, scientists like us tend to do that as a professional habit). Keep your mind open and always remind yourself that your understanding is at best imperfect, as this is as close to the truth as you will ever come as a scientist.

There are other cases in which the phenomenon cannot be understood in macroscopic terms. This is usually when one or more properties are so strongly modified to overwhelm its macroscopic-like behavior. An example is locomotion of nanoscopic objects in fluids, a very hot topic these days in nanoscience. The effect of viscosity at that length scale is so different from what we experience in the macroscopic world that it is very hard to have a good intuition about it. A nanorod propelled in water by an on-board catalytic reaction [14, 15] is like you swimming in molasses; now that is different! Cases like this are when you might have to start with an inside-out approach, climbing your way up from the

color: the color we see depends on the wavelengths of visible light that is absorbed by a material; if changing the size of a material changes the wavelength of radiation it absorbs, then it will appear of a different color

outside-in approach: translating by imagination a nanoscale process as a familiar macroscopic process to extrapolate some predictions over its behavior

hypothesis: the foundation of the scientific method; a supposition that can be disproven by reproducible experiments

inside-out approach: building an understanding based on the widest possible set of details of a material's behavior inside of the problem, starting from the minutest details to get to the big picture. This is usually a painful process as everything should be considered from the beginning and weighed in order to draw any conclusion on the general behavior.

These two approaches can be understood when considering the concept of shape. Shape has profound and subtle effects on the size-dependent properties we talked about in the previous section, but also strongly affects the "macroscopic-like" behavior of nanoscale elements, often in a quite intuitive manner. The reason being that shape is defined by size-invariant concepts which exert their effect irrespectively of the characteristic size of your system.

shape: in nanoscience this affects the relative size-dependent effects in a directional way and the directionality of self-assembly

A relationship between shape and size exists, but it is a result of relative values rather than absolute measurements; for example, a rod has a rod shape because it is longer along one direction than along the other two, measured as an aspect ratio. And this is how and why shape affects size-dependent properties. It allows you to give them directionality. For example, the color of nanoscale metals like gold is determined by the frequency at which the "sea" of conduction electrons can oscillate (such oscillations are called plasmons). Spherical nanoscopic gold (isotropic) is usually red because the conduction electrons have a single frequency at which they oscillate resonantly, thus leading to a pronounced absorption of light at a wavelength of about 520 nm. If the nanoscopic gold is instead rod-like (anisotropic), there will be two different frequencies (transverse and longitudinal) because it has two different sizes: diameter and length (see Figure 1.6). The effect is that the color of gold nanorods is very different, as one of the frequencies

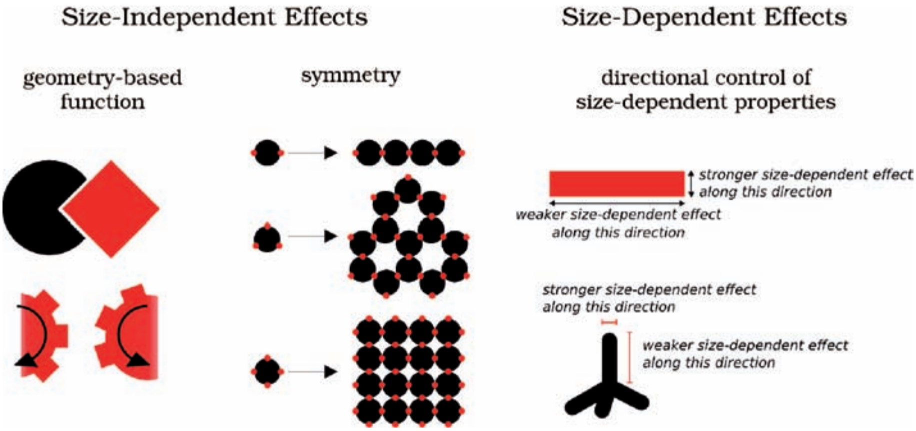

Figure 1.6 Diagram of shape, illustrating its effect on function. We have tried to remain as general and as conceptual as possible in order to ideally include in here as many cases as possible.

(longitudinal) can be tuned to be in the infrared by just changing the aspect ratio of the nanorod.

size-invariant behavior: usually related to a geometrical configuration

Shape in its size-invariant effect has instead mainly to do with how the object interacts with other objects. For example, two gears can be fitted to perform a "geometrical" and dynamical function, which is the transmission of torque. But a gear and a disk cannot do it. The lock and key mechanism is a clear example of size-independent, shape-driven, geometry-based function (see Figure 1.6). It was first developed in the molecular world, when Nature understood that the needed selectivity and efficiency of enzymes could be achieved also by adapting the geometry of their active site to the substrate molecule. Mankind independently discovered the same concept millions of years later and used it to create a nuisance for thieves. So much for progress!

symmetry: this is present if moving an object in a geometrically precise way does not affect its appearance

periodicity: when a structural unit repeats in space at constant spacings

When symmetry comes into the geometry, things get even more interesting. Symmetry can be superficially defined as the property of an object by which a group of rigid geometrical transformations does not change its appearance; a cube can be rotated by 90 degrees without changing the way it looks. When it comes down to nanoscience we realize that, besides influencing subtly a lot of physical and quantistic properties (in a way we have not space to discuss here), symmetry usually induces and determines periodicity in self-assembly (see Figure 1.6). For example, let us say you need a chain of nanocrystals connected together: a one-dimensionally (1D) periodic system. What you will need is for your nanocrystals to connect together only at opposite poles: an example of twofold symmetry! [16] If instead you want your nanocrystals to form a 2D square lattice, they need to connect to other nanocrystals at four spots on a plane separated by 90 degrees: a case of fourfold symmetry (see Figure 1.6). Now that you have seen how to go from periodicity to symmetry, you can also go the other way around! For example, if you see a certain periodicity in a self-assembled system you can usually find that there is an inherent symmetry in the building blocks or in the driving force responsible for the assembly. You can go back and check again Figure 1.4; panel (a) shows a beautiful superlattice formed by nanocrystals; the reason they pack that way (a lattice called face-centered cubic or fcc for short) is due to the fact the particles are roughly spherical, a shape issue, while polydispersity, a size-related issue, mainly determines the distance, on average, at which the periodicity breaks. Panel (b) shows you that nanorods of fairly uniform thickness like to pack parallel to each other, and this again is due to their shape. The properties of the nanocrystal assembly are isotropic (i.e., the same in every direction) while those of the nanorod assembly are anisotropic (i.e., different parallel versus perpendicular to the rod axis). As you can see you have already learnt that self-assembly of nanoscale building blocks in mainly influenced by their

monodispersity: the amount of size homogeneity; in chemistry it is used to describe a set of molecules or particles with identical size

polydispersity: the amount of size inhomogeneity surface, their shape and the homogeneity of their size . . .and we have not yet talked about self-assembly!

When building blocks assemble together autonomously, their shape often determines the architecture they will form; shape in fact determines the directionality of their reciprocal interaction. For example, if two nanorods have a strong affinity for each other's surface, they will not prefer to touch at their tips but they will rather align side by side in order to maximize such interaction. This is a surface-driven effect but it is possible, through creative surface-functionalization chemistry, to coerce the nanorods to form end-to-end strings [17].

nucleation: nucleation and growth are the names by which the different phases in the growth of most nanomaterials are called; for example, ice in freezing water does not form all at once; sometimes you can underfreeze water without any ice forming (think of waterfalls); what you need is to create enough stable nuclei, which are particles of ice large enough to be thermodynamically stable; this initial phase is called nucleation; the later phase is when the remaining material grows on top of the stable nuclei

In the end, whether in the macroscopic or nanoscopic materials world, one has to dream up synthetic methods that can be used to target a particular composition with a specific shape. Nanochemists have learned how to "play the shape game" quite well in the last few years, and you will see a myriad of examples in which chemical command over nucleation and growth can enable shape control of a wide range of materials traversing multiple length scales. Differently from the shape control you might be used to imagine (like the one exerted by a sculptor), chemists prefer to rely on chemical forces to "convince" a material into growing with a specified shape; one uses clever chemistry to enhance the rate of growth of specific crystal facets along particular crystallographic directions with respect to others, tailoring a desired shape. This level of control has brought to an extreme a diversity of nanocrystal shapes.

To summarize, our suggestion is to think of shape, at least regarding its function, as an engineer would think of it: as a tool to create a structure with property. And in this book some of those geometry–property–function relations, as well as our chemical strategies to synthesize shapes will be displayed. As they say, shape is everything in the (nano)materials world, so get ready to shape-up with nanomatter!

1.5
Self-Assembly

Now that you know the basic characteristics of a building block – size, surface, and shape – you can widen your perspective and see how these concepts can be used in a larger context. It is the time for you to think architecture, blueprints, construction, assembly, organization; time to think "big" about building "small".

biomimetics: the emulation of biological processes for the achievement of function and property in artificial systems

One of the paradigm shifts of recent years in science has to do with our attitude towards Nature. At the times of Galileo and Laplace, Nature was something to understand; at the times of Einstein and Faraday, it was something to control. In our times, gradually, Nature is becoming something to learn from. We are slowly coming to understand that our anthropocentric aims are not necessarily compatible with our survival. We are realizing that in practically every case Nature is "smarter" than us, or just does it better. So much for progress, again!

A new vision surfaced in the arena of science as a consequence of this paradigm shift: self-assembly. It is a vision based on the idea of imitating the self-organization phenomena occurring in Nature over "all" length scales; a vision of designed building blocks which will assemble autonomously into an architecture with function. The popularity of this concept is astounding and it begs many questions. Why are we so fascinated by self-assembly? What are we really looking for in it?

Most of us feel an ancestral love for things that grow; the marvel of spontaneous development is undeniable. And while biochemists might be used to it, self-assembly might be the way for chemists, usually relegated to inanimate matter, to satisfy that need.

self-assembly: apparently spontaneous self-organization of objects; it arises as a system strives to find minimal free energy

Besides its philosophical relevance, self-assembly is a difficult concept to pin down [7]. In equilibrium, or when there are no relevant external forces, self-organization proceeds to the energetic minimum, which is determined by the building blocks and is fixed and static. Out of equilibrium, or in the presence of external forces and fields, we can observe dynamic self-assembly; the energy minimum, and thus the structure which is formed, depends on the amount of energy we inject into the system and once this energy is not supplied anymore, the system falls apart. These structures are adaptive; architectures that mutate to adapt to a new environment. The human body is a good example of an exceedingly complex dynamically self-assembled system: the food, the oxygen, the heat are the sources of energy that are necessary to keep our body in good working condition, and when those stop being provided the system "disassembles" (see Figure 1.7).

These two different sorts of self-assembly have different aims. The static self-assembly is generally intended to create a complex architecture for which we envision a certain property, like high surface area for sensing, high strength for protective coatings, low dielectric constant for optical cladding, low thermal conductivity for thermoelectrics, mechanical flexibility for electronic paper, and so on. As we wrote in the previous section, you can initially think of a nano-architecture as if it were in the macroscale, a building that "autoconstructs". Keep in mind concepts like surface area, empty spaces (porosity), structural strength (mechanical properties), surface chemistry (charge, functional groups), and so on. Then you can find the minimal building block you need and try to find a way to self-assemble it into the desired architecture. Be an architect, be creative, think beyond assumptions, play nano!

Nanochemistry is about objects and as such you should be the engineer of those objects. Think of them as your bricks and mortar and find a way to force nature to do the hard work of assembling them for you.

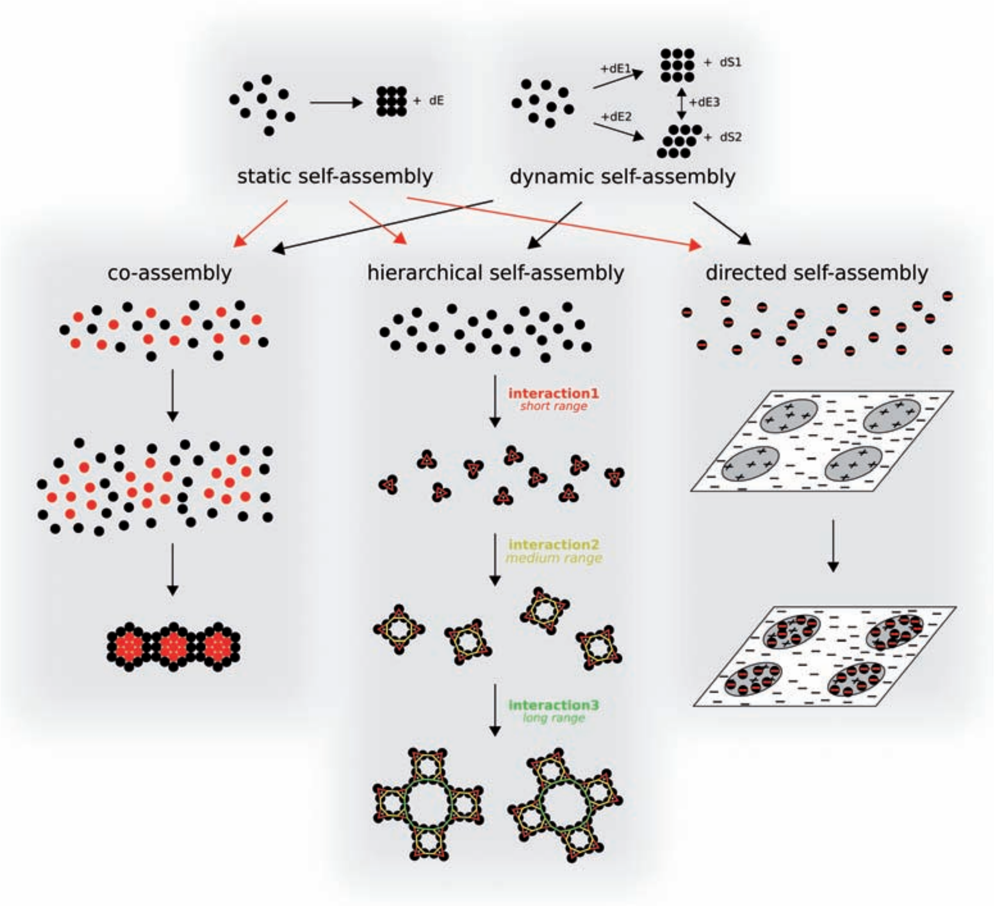

Figure 1.7 Here are depicted the major classes of self-assembly. The borders between them are intentionally blurred to emphasize that the classification is inevitably imperfect. The two main families of self-assembly discussed in the text (static and dynamic) appear at the top (these diagrams are inspired by the work of Bartosz Grzybowsky's group at Northwestern University). They further subdivide into co-assembly, hierarchical self-assembly, and directed self-assembly. These three subfamilies have rather large intersections: systems obtained by hierarchical co-assembly or hierarchical directed self-assembly. Co-assembly is generally defined as a self-assembly process where two or more different components self-assemble contemporaneously and interdependently to form a complex architecture where the two components are usually segregated and not entirely mixed. Hierarchical self-assembly, as explained in the text, is when the fundamental building block is self-assembled in primary structures kept together by short range forces. Such primary structures become then the building block for the self-assembly of secondary structures which happens thanks to different, longer range forces. This process can repeat itself until the highest level in the hierarchy is attained. Nature can easily create architectures possessing even seven different levels of hierarchy. Directed self-assembly instead is when an external force, created and

Static self-assembly is often seen as a cheap way of fabricating complex structures, by using natural forces, and a large dose of wit. Now, considering it only as a cheap version of other fabrication methods is really unfair, since self-assembly can fabricate structures of greatly superior complexity to any other fabrication method we have; self-assembly can easily be 3D, while our widely known top-down nanofabrication techniques are mostly planar by nature, at least for now.[2)] The disadvantage that self-assembly has when compared to the established nanofabrication techniques is that it usually presents defects that are intrinsic and not necessarily desirable; the structures formed are never perfect. This is why you should always keep in mind that the function you look for from a self-assembled structure must be defect-tolerant. This is quite a popular concept these days, all the way from fault-tolerant computers to nanophotonic crystal circuits! Think about our body: when confronted by a defect it will try to correct it, to isolate it, or to adapt to it. Similar flexibility is needed from the new generation of nanotechnology-enabled devices.

static self-assembly: self-assembly determined by the state of minimal free energy in a confined system that energy can neither enter nor leave

defect-tolerance: a design principle by which a device which performs a function can tolerate a certain amount of defectivity in its components; it can also be referred to a property if this property is only marginally affected by a moderate defectivity

Sometimes spontaneous self-assembly is not easy and thus chemists have developed a brute-force method to create complex structures: casting or, in materials chemistry terms, templating, illustrated in Figure 1.8. Sculptors were using this technique hundreds of years ago, but on a different length scale. You find a template (a mold) with holes and you fill them with your material. You consolidate your material and then you remove the template. What you are left with is the negative of the mold, the inverse structure, which is usually an architecture. The process of casting a bronze sculpture from the clay master is an example of templating shape. Sometimes the template itself is a self-assembled material and here things can become really interesting.

templating: using an existing material of a certain shape as a mold to create a negative reproduction in a new material

controlled by us, is used to direct the self-assembly of the fundamental building blocks. In the diagram is shown how a surface patterned with islands of positive surface charge in a sea of negative charge can be used to perform directed self-assembly of negatively charged building blocks to the positive areas. Porous materials with 1-, 2- or 30 voids can also direct the assembly of building blocks to a composite architecture, referred to as host-guest inclusion, more later on this, and see Figure 1.8.

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2) Top-down and bottom-up are two very popular terms among nanochemists. A bottom-up procedure is when you start from the smallest components and you assemble your desired structure from the ground up. Top-down is when you start from a large chunk of material and you cut it and trim it till you get your nanosized architecture. Usually bottom-up is associated with chemistry and synthesis, while top-down is associated with physical processing techniques, like vapor deposition and lithography.

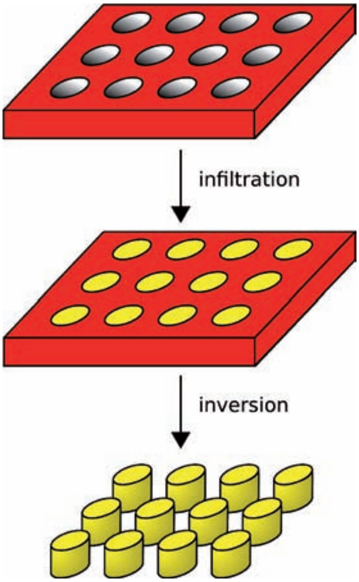

Figure 1.8 The templating strategy is here described. For example, a template possessing holes is first produced. The holes are infiltrated with the material of choice (sol–gel precursor, molecules, polymers, nanocrystals, nanorods, nanowires, etc.) and then the template is selectively dissolved, leaving behind the inverse structure composed of the infiltrated material of choice.

dynamic self-assembly: self-assembly in out-of-equilibrium conditions where the state of minimal free energy is determined by the flux of energy in and out of the system

In contrast, dynamic self-assembly is instead aiming at something very different and more profound. It is aiming at developing adaptive systems; systems which adapt to the environment; systems which learn and that can be literally "turned off" by removing the energy input.

Think now about the implications. Imagine a system which can learn from the environment, by mutating. Imagine the potential of something like this, for example, to solve problems: if these chemical machines can learn something by "studying" their own environment, then we can learn from what they learn! We can have a system in which we can impart a natural selection so that only the best performing architectures are kept and duplicated. Instead of going through implausibly complex numerical calculations, we could build a natural system that would find the solution for us, given enough time.

evolution: natural or artificial creation of optimized living or non-living systems

This vision is not just driven by our desire to have machines that learn for us, it is, we would say, about learning how Nature fails and how it learns from its mistakes, so that we might understand how to handle mistakes better, a much needed quality... Some of you might have played some of those video games in which you can "see" and "direct" an evolving system. What if you could do it in the real world, without quotation marks?

As we write, this is still a vision and we are not yet there, but science can also be about pursuing visions, not only about solving problems. And if you like to solve problems, be sure you will find plenty when you are chasing a vision, believe us.

hierarchical systems: integrated systems built from matter organized at different length scales

You might be thinking that this is already quite amazing, but self-assembly is in the end just a tool. Nature uses self-assembly to go to the next level. Nature is able to self-assemble contemporaneously at many different length scales to create structures that are called "hierarchical". You should not associate this word with the often unpleasant hierarchy you find in most organized communities, including universities. Hierarchy in nanochemistry means the organization of matter at different length scales to create an integrated system, be it chemical, physical, or biological. Building blocks are self-assembled in a primary structure, which then becomes the building block for the secondary structure and so forth, until one reaches the highest level in the hierarchy. At each level the self-assembly is driven by different forces, operating on the larger length scale (see Figure 1.7).

Why does Nature do it? It is a tough question but our opinion is that it has to do with being able to create structures at many different length scales with the same building blocks. Nature is parsimonious! Your smallest building blocks can assemble to form a primary structure. These primary structures will then start to interact with each other using different forces, self-assembling in a secondary structure, and so on. Each of these structures is thus assembling on different length scales using different forces (see Figure 1.7). The final result is often a highly organized material with remarkable properties. A classic example is the amino acid primary module that assembles into protein polymer secondary building blocks that form double helix tertiary units that fold into quaternary structures at the highest level in the hierarchy. We think Nature in its frugality might find this approach practical since it enables the construction of exceedingly complex and large structures from very small and well defined molecular building blocks. It also allows the embodiment of different size- and shape-related properties in the same architecture; for example, the same architecture might be fibrous at a certain length scale, porous at another, and lamellar at yet another.

Why then are we not doing it? The answer is simple: hierarchical systems are very difficult to devise. The procedure of creating primary structures able to undergo spontaneous assembly over several levels is not well understood. And this is one of those grand tasks you might want to contribute to.

ionic crystal: an ordered atomic lattice composed of strongly ionized atoms held together by mainly electrostatic forces; NaCl being the typical example

To make things even more interesting and complicated, you can imagine having building blocks of different kinds co-assemble into a structure. Such co-assembling systems are usually composed of two or more components that synergistically drive each other's self-assembly to completion into a complex architecture (see Figure 1.7). Some talented colleagues at the University of Utrecht [18], IBM [8], and Northwestern University [9], for example, have shown that by tuning the surface properties and the relative size and shape of their building blocks, they could co-assemble mixtures of different nanocrystals and colloids with the same symmetries that different atoms assemble into when forming an ionic crystal (see Figure 1.9).

orbitals: areas of space surrounding the nucleus of an atom or a molecule which are presided by electrons possessing a specified energy and quantum numbers

tailoring: intentionally making materials with the exact range of properties you desire

The interest in such nanostructure assemblies is that most of the time the size-dependent properties are affected by how close together the nanostructures are. As for atoms, whose orbital superposition gives rise to molecular orbitals, in nanostructure assemblies the size-dependent properties change gradually with their respective distance. And it is needless to say that nanochemists have developed, through tailored surface functionalization, phenomenal control on the spacing between nanostructures, down to the Ångstrom level.

boundary-condition thought: pushing an idea to its extreme to test its validity

Thinking about the way the properties change due to coupling gives us a good example of how to use boundary-condition thoughts. Follow us in this example of a powerful reasoning "trick". Non-interacting nanomaterials have properties different from the bulk; this you know. You start putting many of them together and you know their properties change with their respective distance. Now, and this is the key step, we bring the problem to the boundary and we ask ourselves what would happen if the distance would be so small as to be nil! Well, obviously you would not have nanomaterials anymore but a macroscopic chunk of material which has to behave like bulk. Between these two extremes there should be a smooth transition, as Nature does not like sharp transitions (remember what we said about interfaces. . .). In that middle ground of coupling is an interesting form of nanomatter whose properties are in between the nanomaterial and the bulk and depend on the strength of coupling between the component nanomaterials and how they are arranged in the assembly. This coupling will be distance-dependent, which as we mentioned above is under Ångstrom control, and therefore tunable. Tunable coupling, tunable properties, tunable devices!

tunable: when a property of a material can be "tweaked" deliberately by varying one or more parameters

So this teaches you two things: firstly that coupling between nanomaterial building blocks usually brings forth properties intermediate between the nanomaterial and the bulk; secondly, that when you are trying to predict the effect of a change, it is a good idea to imagine the consequence of that change at its limits, where predictions are usually straightforward. "Boundary-condition thoughts" are not always right, but most of the time they give good hints. If you discover that something strongly disobeys their predictions then you have probably found something interesting.

At this point you might be starting to wonder how chemists manage to control self-assembly processes. There are mainly two philosophies

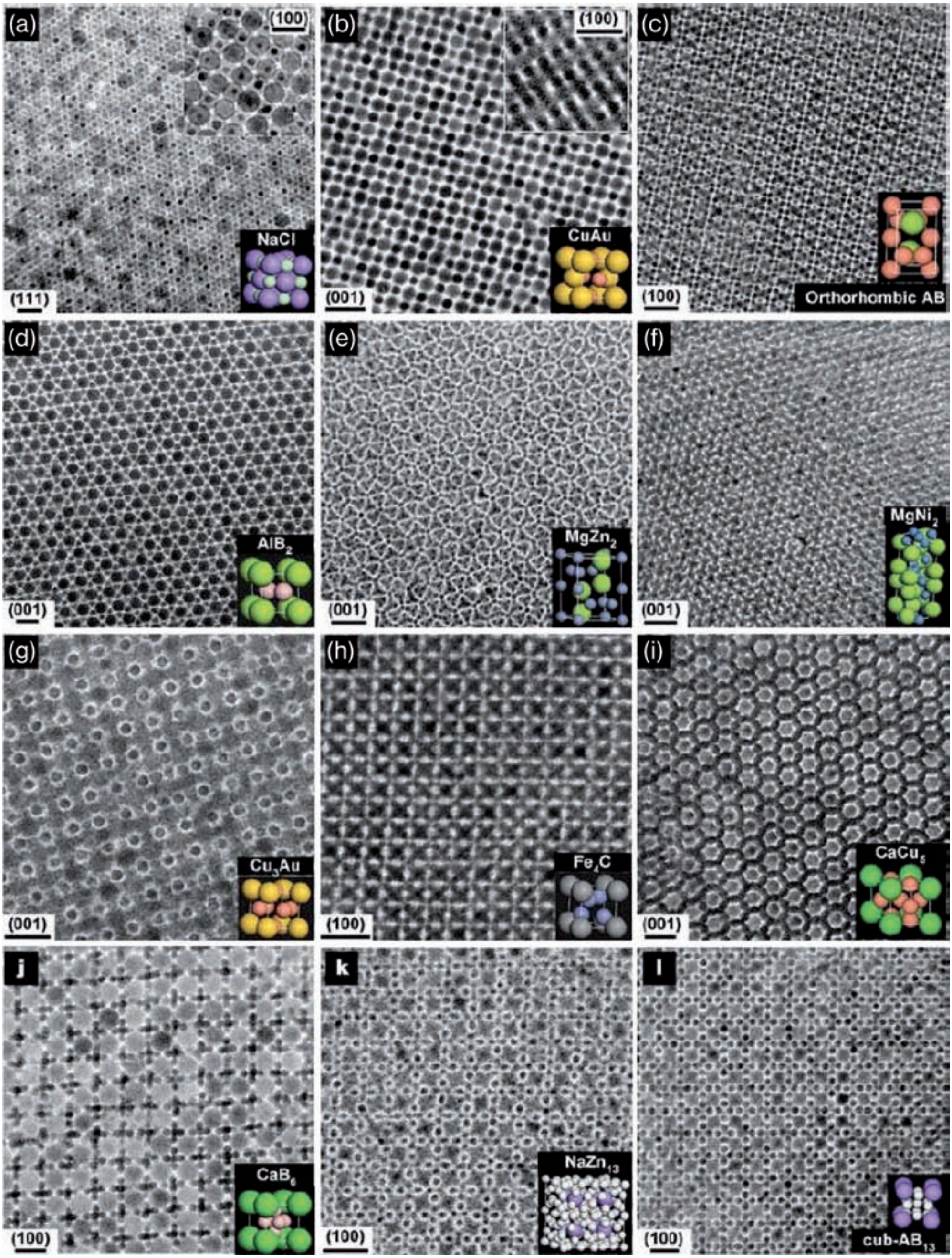

Figure 1.9 Here is shown transmission electron microscopy images of binary lattices obtained from nanocrystals. In the respective insets you find the analog in the standard atomic crystals. Such binary superlattices are composed of nanocrystals of different composition, property and function. The merging of their properties in one single ordered material was a remarkable achievement [8].

directed self-assembly: when external forces are used to guide objects into a desired pattern

that are being followed to achieve complex self-assembling behavior. The first and most ambitious, states that the assembly should be completely autonomous, that the final architecture has to be determined entirely by the characteristics of the building blocks; a bit like the human being, composed of amino acids which are self-assembled according to a blueprint: the DNA, the code of life. The second states that self-assembly can be also directed by using external forces into forming a chosen architecture as we briefly mentioned before. The first philosophy is elegant, as this is the way Nature likes to do self-assembly. It is as yet far too early for us to have such high control of the building blocks even though the first encouraging steps have been taken. The second philosophy, the one of "directed self-assembly", is indeed more common. For example, you might use a liquid flow to convince nanowires to self-assemble into parallel lines; or you might deposit negatively charged particles on specified spots on a surface if you can selectively put a positive charge on those spots (see Figure 1.7). You will see that in nanochemistry most of the self-assembly processes are indeed directed by the chemist-puppeteer.

As a last remark in this long section, we want to remind you that self-assembly is not only a nanoscale phenomenon. Self-assembly happens at every length scale with different driving forces [7, 19]; one can see the cosmos as a self-assembling system under gravitational forces. The specific relevance of self-assembly for nano lies in the great variety of chemical and physical forces that we can use at the nanoscale to trigger and drive it. The other point is that manipulation at the nanoscale is still primitive and likely to remain impractical, so that self-assembly represents a very attractive route to create architectures from nanoscale building blocks.

The scientific community has just started down the research path of self-assembly and there is plenty of room for everybody who wants to contribute. And everybody feels that something amazing lies ahead, in uncharted land where everything you stumble upon is new.

1.6
Two Words About Defects

So far we have mostly given the impression – a false one – that nanostructures might be somehow perfect. But there is no such thing as Santa Claus, you know? And by the same token there is no such thing as a perfect material!

point defects: these occur in a lattice when an atom is missing, misplaced, or different from what it should be

We mentioned that crystals are made of atoms disposed into translationally periodic lattices. The position of these atoms should thus be completely determined. Well, it is not so. Atoms can be missing (vacancies), misplaced, or different from the ones they were supposed to be (impurities). These are called point defects as they concern only single atoms.

Such impurities can bring or remove electrons to or from the solid, thus changing its electronic and optical properties by a process called “doping”. The controlled doping of silicon in electron-deficient and electron-rich areas (called p- and n-doping, respectively) is at the core of present-day electronics. To make these devices function we are not talking about much dopant – parts per million are sufficient to do the trick. But how do you control boron doping in a 1000-atom silicon nanocrystal? Now you can see some synthetic challenges in trying to dope nanomaterials to control their properties and functions!

doping: creating point defects that allow electronic charge to be conducted

Along with point defects there are also linear ones where the position of an entire string of atoms in the lattice is misplaced (dislocations). Such dislocations are at the basis of the mechanical properties of metals as their movement is responsible for their plastic deformation.

line defects: these occur in a lattice when the position of an entire string of atoms in the lattice is misplaced (dislocations)

We can even go one dimension higher again to 2D defects, when a whole plane of atoms is missing or misplaced (stacking faults).

planar defects: these occur in a lattice when a whole plane of atoms is missing or misplaced (stacking faults)

And since most substances are not formed by one single crystal, there will be interfaces between the various crystalline grains. Such interfaces are called grain boundaries and are responsible for many other properties of materials (diffusion properties like ionic conductivity, mechanical properties, etc.). In fact, a so-called perfect single crystal is often a mosaic of smaller ones making up the whole but not quite aligned perfectly with respect to each other. This phenomenon is referred to as mosaicity.

grain boundaries: interfaces between misaligned crystalline grains within a polycrystalline material

These defects can also interact with each other. They can coalesce in defect clusters, assemblies of defects with well-defined shapes and housed within the parent lattice. Impurities in the lattice can also pin down dislocations, and limit their movement thus making the material stiffer. This is the principle behind the enhanced mechanical properties of alloys.

On a more general note, defects can be so extensive that the composition of the material can be affected. When we learn chemistry we are used to thinking that table salt is NaCl and therefore that there must be one sodium atom for every chlorine atom. This is called stoichiometry and is what many non-chemists (and some chemists as well) hate about chemistry. Well, perfect stoichiometry in a solid is an approximation, as all phases of materials are stable in a fairly large spread of compositions (easily 1%). Such non-stoichiometry is an absolutely general phenomenon and it is responsible for many cool materials like transparent conductors, heterogeneous catalysts, ceramic superconductors, and more.

stoichiometry: the ratio of elements in a material

Besides their general importance, the specific relevance of defects in nanostructures is that their surfaces can often be thought of as a defect. We will give you an example. Thermoelectrics are devices that upon *thermoelectrics: devices that exhibit a voltage when exposed to a gradient in temperature, or exhibit a gradient in temperature when a voltage is applied to them*

exposure to a gradient in temperature exhibit a voltage, and vice versa. You can also apply a voltage to them and they will create a temperature gradient. This has phenomenal possibilities in recovering a useful form of energy (voltage) from a mostly useless one (heat). Imagine cladding your car engine (notoriously hot stuff) with such devices and you might power your lights just thanks to the heat produced by it. Quite some energy saving!

Now, the problem of thermoelectrics is that they are very inefficient. The reason is that they need to be made of materials that conduct heat extremely slowly, while conducting electricity very well. And this is a bit of a headache since the electrons, which are responsible for the current, also transport heat. The other contributors to heat transport are the phonons, which are basically quantistic vibrations of the atoms in the lattice; such oscillations propagate well if the lattice is perfect but they get scattered when they meet an imperfection, be it a vacancy, a dislocation, a grain boundary, a surface, and so on.

Nanomaterials are naturally imbued with so many surfaces that their thermal conductivity is extremely sluggish. Phonons get scattered continuously so that their travel to the other side of the device becomes an incredible chore, much like for a ball in a flipper. The conductivity of electrons is instead not so dramatically affected since electrons can hop across interfaces much more effectively than phonons. So, here you have it. Fast electron conduction, slow heat conduction, the perfect thermoelectric. Well, we are getting there. . .just give us a couple more years.

Another effect that the high surface area of nanomaterials has on defects is on stoichiometry. For example, you can have a 5 nm PbS nanocrystal on which the surfaces are preferentially terminated with Pb. This can be achieved pretty easily and we will see how later. Since for a 5 nm crystal the atoms on the surface account for half of all the atoms, this means that the stoichiometry of a nanomaterial will be very different from Pb_1S_1, and instead be more something like $Pb_{1.15}S_{0.85}$. Non-stoichiometry is a general aspect of materials, but this is especially true and remarkable for nanomaterials.

Other kinds of defects, like vacancies or impurities are instead remarkably rare in nanomaterials; given the high surface energy of nanostructures, point defects are usually segregated to the surface where they can reduce the surface energy. This means that nanocrystals are often free from point defects or impurities.

In conclusion, just as in bulk materials or indeed any other matter of life, defects in nanomaterials have to be kept in mind, as they are ubiquitous. Some of them can be eliminated by controlling the conditions of growth of the nanomaterial (increasing the temperature and/or slowing down the growth speed), while some others are intrinsic and so they are part of the thermodynamic equilibrium of the system.

But who says that materials or nanomaterials need to be in thermodynamic equilibrium in order to exist? Metastable materials are thermodynamically unstable phases of matter but they can exist for centuries as their stability is determined by kinetics, the rate at which they transform into the stable form, a common example being glass. But we are digressing here...

1.7
The Bio–Nano Interface

If you are a biochemist, after reading these pages you could likely ask: "So what?" You might already know that your systems do not show size-dependent behavior and so you wonder why should you even read this stuff; why should you read about nanocrystals and nanowires, when your biological systems are so much more complex and cool, and they self-assemble without you having to sweat one drop? Why should you even care about inanimate and cold matter?

Ok ok ok, we know...but wait a second. What if we tell you that we can make a nanomaterial that can be dispersed into your blood, that selectively attaches to cancer cells making them detectable, and that, when illuminated by a mild laser, can actually burn the tumor and not affect your skin or healthy cells? That sounds more interesting now, doesn't it?

Well, this is really only the tip of the iceberg. At the moment of writing, the so called bio–nano interface probably holds more promise than any other application of nanoscience. So, we are really excited about telling you why.

The main idea is that nanomaterials have a size which allows them to interact directly with biological processes and structures. This means, for example, that I can use my luminescent nanocrystals to track the movement of proteins or cells. I can attach specific molecules to the surface of my nanostructures so that they bind with specific tissues. I can design nanoarchitectures that stimulate and direct the growth of cells so that a wound or a broken bone can be regenerated. And I can deliver a nanocapsule of a pharmaceutical to a site of disease to cure the ailment.

The refined control of size, shape, architecture, and surface chemistry that we have achieved allows us to create materials which can interact in a tunable way with the biological world. We can now bring the materials world we know so well close to the molecular scale where biological processes operate. And, by doing this, we can achieve things that were deemed unthinkable only twenty years ago.

The health funding agencies are mostly interested in diagnosis and treatment of diseases and improvement of bioanalytical techniques but you should never forget that the enormous potential of nanoscience, especially when coupled to biology, can be used with less noble intents.

legacy: something passed on to future generations

You cannot afford to be naïve, but you should not be scared of the future either. The stereotypical picture of the scientist so focused on his own curiosity as to forget the consequences of his discoveries is partly true. But as we get closer and closer to the illusion of being absolutely in control, scientists should be more and more outspoken on the dangers that such illusions might bring forth. You can be a modern day Pontius Pilate, and likely be remembered as such, or you can be aware, alert, and outspoken, and be remembered as a voice of reason. It is really up to you.

Science "will" determine the future, especially in the face of of the amazing environmental and medical challenges that are confronting the world. Your own work could make a wonderful or a terrible difference. You should think about Ian Fleming, discovering penicillin and literally saving millions of people, as that is the kind of difference one single scientist (or much more likely a group of them) can make for the good, but potentially also for the bad. You might be interested in reading about the life and work of Fritz Haber, which we think best embodies the disruptive potential that scientific endeavors can have.

Returning to the easy track, as we said in the subchapter on Size, everything has a characteristic length scale, and your materials show it or are affected by it in a different way, depending on their size. Biology also possesses length scales and as such your materials can interact with it differently. Based on such interactions, several different trends have emerged in bionano.

proteomics: the study of the workings of proteins in cells

The first is to use nanomaterials for analytical purposes. One of the great challenges of our times in biology, and one that funding agencies like the National Institutes of Health (NIH) are pouring money into, is to identify and explain the real inner workings of the cell, more specifically the identity, chemical structure, concentration, and detailed mechanistic function of proteins. This challenge has been dubbed proteomics and is one of the holy grails of modern biochemistry [20, 21]. It is probably not going to be the full picture as our body is a synergetic system in which the ensemble is more than the sum of its parts, but it would help us greatly in understanding the origins of disease and aging.

The problems associated with proteomics are many and are mostly related with the small concentrations of many fundamental proteins in our organism; this makes them difficult to isolate, characterize, and follow as they go about their routine jobs in the cell. The extraordinary surface area of nanomaterials and the susceptibility of their properties to their surface chemistry make them a natural choice for ultra-sensitive sensors.

The main results in this area of research are based on two concepts; in the first approach a detecting molecule with extremely high specificity is attached to the surface of a nanomaterial; upon binding of the analyte to the sensing molecule a determined property (like conductivity) of the nanomaterial is changed and detected, signaling the binding; this is a common route for nanowire sensors [6].

The other approach relies on the change in color of nanoscopic gold (from red to blue) upon aggregation [22]; if the analyte is made to attach to two different nanocrystals at the same time, this will lead to aggregation, which will be signaled by a color change. The color, as mentioned before, comes from plasmon resonances which originate from the oscillation of the free electrons on the surface of the metal. Anything which binds or comes close to such an oscillating cloud of electrons, like another metal nanoparticle, changes its frequency, often dramatically. Related, but different, are surface-enhanced Raman spectroscopy (SERS) signals emanating from analytes bound to metallic nanostructures and nanoscale rough metallic surfaces. These gigantic SERS signals, rather than the normal puny Raman signals we have come to expect of molecule vibrational signatures, are also created by plasmons. Such rapid conduction electron oscillations generate huge electric fields that efficiently excite the Raman spectrum of any molecules in close proximity or bound to the surface of the metal (a famous example being silver). These enhancements can be as large as 12 orders of magnitude over the normal Raman intensity and play a major role in enabling sensing and diagnostics in bionano systems down to the single-molecule level [23].

analyte: a chemical substance that is subject to analysis

surface-enhanced Raman spectroscopy: an anatytical technique that uses the amplification of the Raman vibrational spectra of molecules adsorbed on metal nanoparticles or rough metal surfaces

To summarize, the bioanalytical approaches employing nanochemistry are mostly based on monitoring the change of the properties of a nanostructure upon binding of the analyte or upon coupling induced by the analyte (see Figure 1.10).

Another monumental challenge of medicine, in which nanochemistry will definitely play a role, is molecular imaging [24]. This is part of the necessity of tracking single molecules in cells to follow their movement and deduce their function. The whole idea is based on attaching a probe to your target so that you can visualize its movement in the cell. The final objective described here is a long term one, while an earlier result will be the targeting of specific tissues, like tumors or plaques.

molecular imaging: monitoring the movement of a target molecule by using an attached probe

The impact of such a result would be enormous on clinical practice, and on the prevention of pathologies; one of the great limits of prevention of cancer and most vascular diseases is the limited resolution of the imaging techniques. And while prevention is the most economically attractive solution to pathologies, it requires screening of the population (hence fast exams and/or cheap instrumentation) and the possibility to detect the pathology at its earliest stages (hence high selectivity, sensitivity, and resolution). While on one side there is a phenomenal engineering research effort devoted to improving the

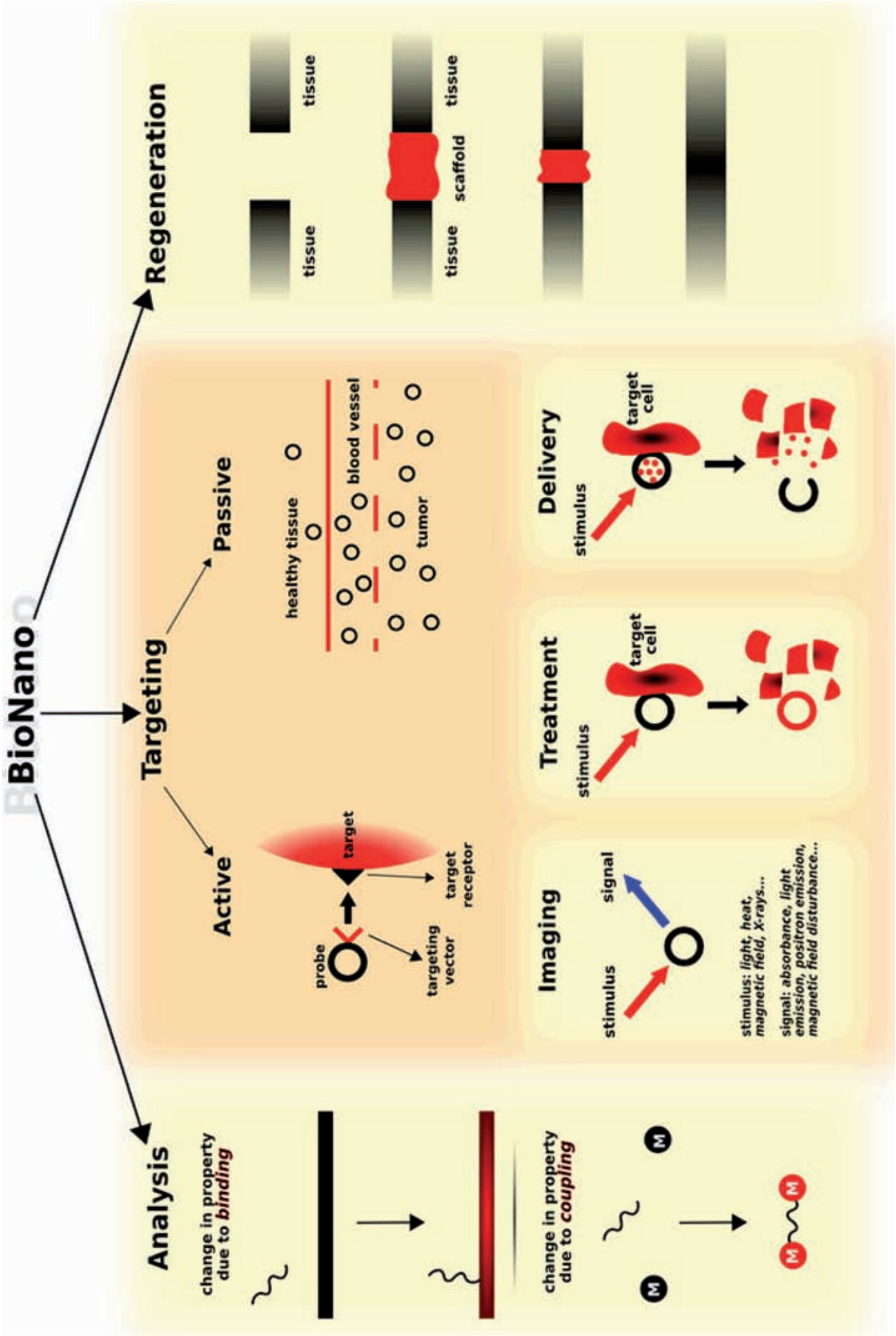
BioNano
Analysis
change in property due to binding
change in property due to coupling
M
M
M
M
Targeting
Active
probe
targeting vector
target
target receptor
Passive
healthy tissue
blood vessel
tumor
Imaging
stimulus
signal
stimulus: light, heat, magnetic field, X-rays...
signal: absorbance, light emission, positron emission, magnetic field disturbance...
Treatment
stimulus
target cell
Delivery
stimulus
target cell
Regeneration
tissue
tissue
tissue
scaffold
tissue

Figure 1.10 BioNano and the major paths of research it has taken The three main fields are bioanalytics, targeting (with purposes of imaging, treatment, or delivery), and regeneration (e.g., tissue, organ, bone, and cell). Analysis is usually accomplished by measurement of a property of a nanostructure which is modified upon exposure to the analyte. Often such property is the color or the conductivity. Targeting is accomplished in an active or passive way. In the former a targeting vector is attached to the probe (which can be a nanocrystal, a micelle, or other nanostructures) and in this way it specifically attaches to a receptor of the target. The passive targeting employs usually the enhanced permeation and retention (EPR) effect according to which tumors possess very leaky blood vessels, when compared to healthy tissue. In this way nanocrystals can be segregated in the tumor just due to such leakiness. After targeting, the probe can have different functions. It can work as a contrast agent and thus allow tissue-specific or even molecular imaging; it can work as a thermal therapy agent if the external stimulus leads to a heating of the probe; and it can also be used as a delivery agent, if drugs can be encapsulated or bound to it. Regeneration strategies are instead usually employing a scaffold which is inserted in the fracture or wound. Such a scaffold encourages the regeneration of the tissue providing them for the right geometrical constraints and supports, while biodegrading in the meantime. Often the bionano strategies are mixed, as regeneration routes are often using scaffold, which includes delivery devices in order to stimulate the tissue to regenerate faster than they would in a natural way. Or a probe can be made multifunctional so that it can be used as contrast agent as well as agent for magnetothermal or photothermal treatment.

instruments (where materials also play a huge part), the other side of the problem is attacked by the development of new contrast agents, namely probes, which are injected in the bloodstream and that can increase the sensitivity of the imaging techniques. Such new contrast agents are becoming more and more based on nanoparticles with different properties, depending on which instrument they are supposed to work with. Regarding computed tomography (CT), for example, the recently developed Bi_2S_3 nanocrystals show a fivefold improvement in contrast, when compared to the iodinated molecules used nowadays in clinical practice [25].

drug delivery: when a therapeutic drug is brought by a carrier to the specific site in the body where it is needed to effect treatment

On the treatment side, it is usually agreed that the ideal picture would be to have a very effective drug, delivered exclusively to the diseased site or tissue where it can unleash its full effect. Let's make a comparison with warfare. If you are trying to destroy a building in the middle of the city you have two choices. You can have a "smart" bomb that is "attracted" by the target and hits it without damaging the surrounding buildings, or you can carpet bomb, with well-known side effects. It is sad to say that most of our pharmacology today is done by carpet bombing (think about chemotherapy); highly toxic drugs in huge doses are administered in order to target a small part of the organism, when only a minuscule amount of the same drug would be needed if it could be directed to the right place. The idea of creating vessels that bring the drug to the target and release it is behind the concept of drug delivery, which was pioneered by Robert Langer at MIT [26]. Another advantage of drug delivery is that it can allow the tailored administration of the drug and thus maintain the right level of concentration at the target, without risks of insufficient or excessive dosages. This predetermined delivery program of the drug to a desired location could be orchestrated to be continuous, graded, or pulsed, indeed whatever makes sense to achieve the desired clinical outcome.

stimuli-responsive materials: materials that change their properties (e.g., color, porosity, shape) in response to external stimuli (e.g., light, pH, magnetic field)

On this side enormous efforts have been carried forward to develop sophisticated carriers for drugs which can safely bring the drug to the site. The challenge for a nanochemist lies in developing a porous nanoarchitecture that can squeeze out what it carries in its pores in a programmed mode, as a response to an internal or external stimulus. This task is complicated, as the bloodstream can be a really aggressive environment for something which does not belong there. Our body is very well equipped to dismantle and process any sort of entity which is recognized as "foreign". It is no joke that some of these vessels that scientists have developed have been dubbed "stealth liposomes" because the molecule which is used to coat them makes them slippery and invisible to the proteins in the blood, which would otherwise dismantle them [27].

Bionanochemistry though is not limited to analysis, detection, and delivery. Nanostructures in fact can be directly used as therapeutic agents! You might remember that we mentioned that nanoscopic metals like gold present a strong absorption in the visible or in the infrared depending on their shape and size. Well, since gold nanoparticles in general are not luminescent, the energy which is absorbed has to go somewhere and in this case it is released as heat. A strategy (called "photothermal treatment") that is becoming more and more promising is to use size- and shape-controlled nanoscopic gold particles as nanoscopic heaters inside the body. When functionalized to target cancer cells, their exposure to an infrared laser beam through the skin can induce an extremely localized heating which can lead to cancer cell destruction (see Figure 1.10). This methodology has already been successfully applied and the damage to the healthy cells is often minimal [28].

photothermal treatment: destroying cancer cells hyperthermally, using heat generated from light-activated reactions or transitions

A similar result can be obtained with magnetic nanocrystals, since magnets tend to heat up in an oscillating magnetic field [29]. You can imagine the advantages of this approach. Laser light can penetrate a maximum of a few centimeters in the tissue, depending on the wavelength. Magnetic fields instead can penetrate the whole body allowing for the non-invasive treatment of cancer in deep tissues. The cleverly surface-bio-functionalized magnetic nanocrystal is key to the success of this amazing new cancer therapy!

The last three directions in research we mentioned (molecular imaging, treatment, and delivery) are all dependent on the possibility to target specific organs, tissues, bones, or cells with nanostructures. Such targeting can be active or passive. Active targeting is accomplished by attaching a targeting vector to the nanostructures which would specifically attach to the target. The passive targeting is using the leakiness of tumors' vessels to segregate nanoscopic probes into the malignant tissue (see Figure 1.10) [30]. It is not worth at this stage to get into too much detail as targeting strategies can vary widely depending on what is the target and what has to be delivered.

Even with this limited perspective it is clear how important it is at the moment to develop more and more specific and efficient targeting strategies for the most diverse targets, so that imaging, treatment, and delivery can all be accomplished with much better results.

The last but not least of the directions bionano is taking is that of regenerative medicine. Definitions are controversial (as usual) but we think a very nice one is that regenerative medicine encompasses all those methodologies through which we encourage and direct the body to regenerate itself. It is a fantastic field, which started as tissue engineering, of which one of the pioneers was again Robert Langer, and that is now developing into a more varied class of techniques, which often overlaps with drug delivery [31]. The idea is that by providing the organism a porous scaffold upon which the cells can replicate, and propagate, the body will be convinced that it has a chance to repair the

tissue engineering: introducing a porous scaffold to the body at a damaged site to encourage cells to replicate and propagate; tricking the body into healing itself wound and it will start regenerating. Sometimes, the body just needs a certain architecture, a certain geometry, while in other cases it also needs some very specific chemical stimuli (like growth factors) and biological instruction (stem cells), which are usually embedded into the porous scaffold whose surface is often functionalized with molecules that improve the adhesion of newly formed cells (see Figure 1.10).

scaffold: a framework that is used to build a larger structure; a tissue scaffold is used as a platform for cell proliferation

Such porous structures present chemical challenges to the bionanochemist as they need to fulfill a series of requirements; they have to be biodegradable and non-toxic, and they have to degrade if possible at the same rate at which the tissues are regenerating. In addition, the scale and geometry of the structure and the distribution of the stimuli on its surface both play a fundamental role; a lot of ingredients have to be present at the same time so that the regenerated tissue is functional. Sometimes in fact, the body is convinced to regenerate only partially so that the final new tissue is not viable. Phenomenal results have already been obtained like recovery of vision or motility in mice with a severed optical nerve or spine, and recovery of vascularization [32]. At an even more advanced stage are scaffolds for the regeneration of bone and cartilage. There is absolutely no need here to stress how important these results might be.

Especially important is that many of these applications of nanoscience can lead to a reduction of the costs of patient treatment. Regeneration is an example, improved imaging techniques is another. This consideration might sound brutally pragmatic, as if the health of a person could be given a price. But as a matter of fact it does, and this is why regenerative medicine has the potential to be extremely useful for developing countries, where the costs of medical treatment and facilities are just too overwhelming to be considered; millions of people remain without adequate health care because of this. Reducing the costs of health care and improving its effectiveness are two of the main objectives a scientist should consider. Giving the possibility to developing countries to afford independent and efficient health care could save millions of their people, better many economies, and often contribute to easing social tensions.

breakthrough: a sudden advance in technology or understanding of Nature

While you might be used to thinking that new technologies are inherently more expensive, this is because they are usually based on incremental improvements; real breakthroughs solve a problem from a completely new direction, thus often reducing drastically the costs of innovation and technology. Such breakthroughs are very likely to happen now in nanomedicine where completely new approaches to diagnosis and treatment of disease are being explored.

So, you have now the exciting opportunity to make a statement and help fight the problems of millions of people, also in your country, by providing instruments to doctors that they could have only dreamed about a few years ago [33–35]. The message thus is that you can not only contribute, but that you can make a difference with science, a huge difference.

What we have summarized here is likely to be only the starting point to a true revolution in the field of biochemistry and medicine; but the extent of this revolution will be dependent on the results of the safety assessment research that will be detailed next. Remember that Nature never gives anything for free; there is always a price to pay for something you achieve. It is just a question of what the price is, if you can afford it, and if you are willing to pay that price.

1.8
Safety

As you might have already noticed from some articles in the press, there is a growing concern about the possible safety issues related to nanomaterials. This is a situation that should make everybody think, especially a student.

Science is mainly a self-governing (or maybe we should say self-*un*governing), individualistic human phenomenon and scientists are an unruly lot. It is not by chance that Richard Feynman, the forefather of nanotechnology, defined science as “the belief in the ignorance of the experts.” A discovery is always about subverting authority and fighting the prevailing view. This obsession for rationality and subversion of assumptions has led some scientists to defend their intuition even in front of overwhelming powers; examples include Galileo Galilei or Giordano Bruno, who were respectively exiled and burnt at the stake as heretics for their defense of reason.

Richard Feynman: the American physicist generally quoted as the philosophical father of nanotechnology

When faced with the opening of a new field of research, scientists can swarm it like grasshoppers. Few think about consequences, few think about a slow step-by step advancement which would cover all the blind spots, when a big zesty result is at hand. This is largely unavoidable and a direct consequence of human curiosity, which is so well represented by the dwarves of Moria in the Lord of the Rings. As fantastically depicted in Tolkien’s masterpiece, digging into the secrets of Nature can have side-effects. The question is thus: “are we going to discover a Balrog of bionano?”

The assessment of consequences, even though it might sound like cleaning the dishes after a large meal, is a necessary and fundamental task, which requires great research skills and rock-solid professional ethics.

ethics: system of morals or rules of behavior

Safety is part of these consequences. The main issue you should keep in mind in the assessment of nanomaterials safety lies in their standardization. There are thousands of different nanostructures that can be produced in the lab according to the literature, and most of them

standardization: a process whereby standards are established are extremely sensitive to the synthetic conditions; PbS nanocrystals produced in our lab are probably slightly different from the ones produced in another lab, even if the "recipe" we are following is the same. It can be a difference in surface charge, in impurity concentration, size, shape, and so on. Even within the same dispersion of nanocrystals there is a distribution of properties, sizes, shapes, surfaces; even one atom difference might make a difference to the properties. All these aspects have influence on their safety profile, an influence we do not know and we cannot really directly measure since we cannot generally produce perfectly uniform nanomaterials!

While in normal pharmacology we are dealing with very well defined molecules which can be purified to an extremely high degree, in this case we are dealing with much more complex entities with an infinitely larger degree of variability.

Several research groups are at the moment dealing with the safety assessment of available nanomaterials, while other groups are looking into the standardization of nanomaterials synthesis, where, for example, the reaction is accomplished in spatially and geometrically well-defined microchannels in a microfluidic chip and the "human factor" should be taken out of the equation, thus leading to improved reproducibility, and more uniformity in properties and standardization of samples [36, 37].

toxicity: extent of harm caused to an organism on exposure to a substance

The challenge of assessing the impact of nanostructures on our health is huge, as the large number of synthetic nanostructures is discouraging, and coordinating a systematic work of characterization among university research labs which are fundamentally independent in their choices is very difficult. But this only means that a few key structures with great promise will have to be first investigated in detail, in order to arrive at conclusions as soon as possible. From those initial investigations we might acquire some guidelines on the design of non-toxic or less toxic alternatives.

Another objective is the development of nanostructures that can be processed by the human body. For example, if we are able to create nanoparticles that would circulate in your body only for a few hours and then be completely expelled or dismantled into non-toxic subcomponents, then the toxicity requirements would be much lower than for particles which tend to accumulate in the liver or in the lymph nodes as they usually do.3)

As we wrote earlier, safety assessment needs exceptional skills as a researcher, because it requires you to work in a multidisciplinary

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3) The liver and lymph nodes are the filters of the organism. It is known that non-biological object of a certain size (this is debated but it should be around 10 nm) will be sequestrated especially in the liver, the spleen and the lymph nodes. Such problematic biodistribution is controllable by changing the size, the shape, and the surface properties of the nanoparticles even though it is not yet completely clear how.

environment on very complex systems with many parameters to control. It also requires strong professional ethics as the topic of this research is plausibly seen as an obstacle to a potential trillion-dollar global industry. This sort of thought is in line with an old school of thinking which needs to be overcome, in the interest of final "customers": why not find creative and rigorous ways to establish a business out of safety assessment? Why not create "interests" which are in the interests of customers? It seems this challenge now is being taken up by many researchers, and funding agencies are financing such enterprises.

Remember that problems always have a solution. To find it is sometimes a question of wit, sometimes a question of courage, sometimes a question of luck, and always a question of determination. We firmly believe then that it is possible to have a safe nanotechnology industry producing groundbreaking and life-saving products. It will be also up to us as scientists to be the watchdogs of this process, holding at bay the drive to obtain commercial results and profit at all costs, and focusing on the long term, where, by professional habit, we should tend to look.

In the meantime, it is our conviction that all nanomaterials should be handled as highly toxic chemicals. There is no safe nanomaterial until proven otherwise. Dry powders of nanostructures must be avoided in the open, as they can be inhaled (remember that asbestos is a natural occurrence of nanowires) and also are potentially explosive and inflammable. Dispersions are less dangerous. Handling should always be performed with goggles, appropriate gloves, and lab coats.

We do not think we need a new series of safety procedures for nanostructures. The protocols for handling highly toxic chemicals are meant to prevent us from getting into in contact with toxic molecules. There is no reason so far to believe they should not work for larger moieties. Chemists have turned safety in the lab environment into a form of art, with many labs around the world handling incredibly dangerous substances in near-absolute safety. Safe handling of materials is one of the requirements for most job positions in the chemical and pharmaceutical industry, with very thick safety manuals to prove it, so use every opportunity you have to learn it. We know being safe is not the top priority for many young researchers, but believe us when we say that it does demonstrate maturity and professionalism, two things which count more than any line in a curriculum. Chances are you will be hired in a company doing safety assessment of nanomaterials. You never know!

References

1 Ashcroft, N. W., Mermin, N. D. (1976) *Solid State Physics*, Brooks Cole.

2 Roduner, E. (2006) *Nanoscopic Materials: Size Dependent Phenomena*, Royal Society of Chemistry.

3 Goldstein, A. N., Echer, C. M., Alivisatos, A. P. (1992) *Science*, **256** (5062), 1425–27.

4 Decher, G. (1997) *Science*, **277** (5330), 1232–37.

5 Kresge, C. T., Leonowicz, M. E., Roth, W. J., Vartuli, J. C., Beck, J. S. (1992) *Nature*, **359** (6397), 710–12.

6 Wang, W. U., Chen, C., Lin, K. H., Fang, Y., Lieber, C. M. (2005) *Proc. Natl. Acad. Sci. U. S. A.*, **102** (9), 3208–12.

7 Whitesides, G. M., Grzybowski, B. (2002) *Science*, **295** (5564), 2418–21.

8 Shevchenko, E. V., Talapin, D. V., Kotov, N. A., O'Brien, S., Murray, C. B. (2006) *Nature*, **439** (7072), 55–59.

9 Kalsin, A. M., Fialkowski, M., Paszewski, M., Smoukov, S. K., Bishop, K. J. M., Grzybowski, B. A. (2006) *Science*, **312** (5772), 420–24.

10 Malakooti, R., Cademartiri, L., Akcakir, Y., Petrov, S., Migliori, A., Ozin, G. A. (2006) *Adv. Mater.*, **18** (16), 2189–94.

11 Cademartiri, L., Montanari, E., Calestani, G., Migliori, A., Guagliardi, A., Ozin, G. A. (2006) *J. Am. Chem. Soc.*, **128** (31), 10337–46.

12 Alivisatos, A. P. (1996) *Science*, **271** (5251), 933–37.

13 Faraday, M. (1957) *Philos. Trans. R. Soc. London*, **147**, 145–81.

14 Paxton, W. F., Kistler, K. C., Olmeda, C. C., Sen, A., St Angelo, S. K., Cao, Y. Y., Mallouk, T. E., Lammert, P. E., Crespi, V. H. (2004) *J. Am. Chem. Soc.*, **126** (41), **13**, 424–31.

15 Fournier-Bidoz, S., Arsenault, A. C., Manners, I., Ozin, G. A. (2005) *Chem. Commun.*, **4** 441–43.

16 DeVries, G. A., Brunnbauer, M., Hu, Y., Jackson, A. M., Long, B., Neltner, B. T., Uzun, O., Wunsch, B. H., Stellacci, F. (2007) *Science*, **315** (5810), 358–61.

17 Nie, Z. H., Fava, D., Kumacheva, E., Zou, S., Walker, G. C., Rubinstein, M. (2007) *Nature Mater.*, **6** (8), 609–14.

18 Leunissen, M. E., Christova, C. G., Hynninen, A. P., Royall, C. P., Campbell, A. I., Imhof, A., Dijkstra, M., van Roij, R., van Blaaderen, A. (2005) *Nature*, **437** (7056), 235–40.

19 Ozin, G. A. (1992) *Adv. Mater.*, **4** (10), 612–49.

20 Aebersold, R., Mann, M. (2003) *Nature*, **422** (6928), 198–207.

21 Pandey, A., Mann, M. (2000) *Nature*, **405** (6788), 837–46.

22 Elghanian, R., Storhoff, J. J., Mucic, R. C., Letsinger, R. L., Mirkin, C. A. (1997) *Science*, **277** (5329), 1078–81.

23 Kneipp, K., Wang, Y., Kneipp, H., Perelman, L. T., Itzkan, I., Dasari, R., Feld, M. S. (1997) *Phys. Rev. Lett.*, **78** (9), 1667–70.

24 Weissleder, R., Mahmood, U. (2001) *Radiology*, **219** (2), 316–33.

25 Rabin, O., Perez, J. M., Grimm, J., Wojtkiewicz, G., Weissleder, R. (2006) *Nature Mater.*, **5** (2), 118–22.

26 Langer, R. (1998) *Nature*, **392** (6679), 5–10.

27 Allen, T. M. (1994) *Trends Pharmacol. Sci.*, **15** (7), 215–20.

28 Huang, X., El-Sayed, I. H., Qian, W., El-Sayed, M. A. (2006) *J. Am. Chem. Soc.*, **128** (6), 2115–20.

29 Hergt, R., Andra, W., d'Ambly, C. G., Hilger, I., Kaiser, W. A., Richter, U., Schmidt, H. G. (1994) *IEEE Trans. Magn.*, **34** (5), 3745–54.

30 Maeda, H., Wu, J., Sawa, T., Matsumura, Y., Hori, K. (2000) *J. Controlled Rel.*, **65** (1–2), 271–84.

31 Langer, R., Vacanti, J. P. (1993) *Science*, **260** (5110), 920–26.

32 Rajangam, K., Behanna, H. A., Hui, M. J., Han, X. Q., Hulvat, J. F., Lomasney, J. W., Stupp, S. I. (2006) *Nano Lett.*, **6** (9), 2086–90.

33 Mnyusiwalla, A., Daar, A. S., Singer, P. A. (2003) *Nanotechnology*, **14** (3), R9–R13.

34 Salamanca-Buentello, F., Persad, D. L., Court, E. B., Martin, D. K., Daar, A. S., Singer, P. A. (2005) *PLoS Medicine*, **2** (5), 383–86.

35 Singer, P. A., Salamanca-Buentello, F., Daar, A. S. (2005) *Iss. Sci. Technol.*, **21** (4), 57–64.

36 Chan, E. M., Mathies, R. A., Alivisatos, A. P. (2003) *Nano Lett.*, **3** (2), 199–201.

37 Yen, B. K. H., Stott, N. E., Jensen, K. F., Bawendi, M. G. (2003) *Adv. Mater.*, **15** (21), 1858–62.