Bioinspired synthesis as a potential green method for the preparation of nanomaterials: Opportunities and challenges
Siddharth V. Patwardhan\textsuperscript{a}, Joseph R. H. Manning\textsuperscript{a} and Mauro Chiacchia\textsuperscript{a}

Inorganic nanomaterials are widely used in e.g. healthcare, electronics and energy sectors (worth several billion $), but their manufacturing is highly wasteful and hence unsustainable. This review highlights the key reasons that make these manufacturing routes unsustainable. We present alternatives, with special emphasis on bottom-up techniques. Biological and bioinspired routes feature as emerging solutions that can be sustainable yet with the ability to produce high-value nanomaterials. Finally, the review identifies future challenges in developing these routes such that they become commercially attractive manufacturing methods.

Addresses
Green Nanomaterials Research Group, Department of Chemical and Biological Engineering, University of Sheffield, Mappin Street, Sheffield S1 3JD, UK

Corresponding author: Patwardhan, Siddharth V. (s.patwardhan@sheffield.ac.uk)
\textsuperscript{a}www.svplab.com.

Current industrial methods
At present, nanomaterials are manufactured using top-down (lithography, milling, and etching) or bottom-up (vapour deposition, sol–gel, precipitation, pyrolysis, solvothermal) approaches \cite{3,4}. Top-down approaches predominate current manufacturing processes for nanomaterials. On the other hand, bottom-up approaches such as hydrothermal or sol–gel synthesis are less widely used despite their promise to help achieve better reaction rates and produce bespoke materials by building them from molecules. Despite their current use and promise, existing methods for manufacturing nanomaterials suffer from following issues pertaining to sustainability \cite{4}.

The main issues include the need for ultrapure precursors, reagents and solvents, which require high energy for purifying reagents. Specialised environments such as high temperatures or ultrahigh vacuum are often required, leading to additional cost and energy. Current methods also either use or produce toxic or hazardous chemicals. Resource efficiencies are poor with typical yields of 3–10\%, which is exacerbated by sequential processing steps, where waste produced multiplies. These issues dictate high consumption of water and energy, creating an enormous burden on the environment and result in unsustainable manufacturing.

Over the last 15 years, the integration of tailored holistic tools such as life-cycle analysis and risk assessment have led to better evaluation of the environmental and safety impact during the use of some widespread nanomaterials such as silver, silica, and titania nanoparticles \cite{5,6}. Despite their preparation being very wasteful and environmentally damaging, most attention aside from material performance has been mainly focused on the toxicity of nanomaterials \cite{7}, while the environmental burden of the synthesis/manufacturing process is largely ignored \cite{8,9}. Environmental impact and sustainability analysis performed using E-factor (waste to product ratio) illustrates the issues highlighted above. It was revealed that the current nanomaterials production methods produce up to 100,000 kg waste per kg product, which is up to 1000 times more wasteful when compared to the production of pharmaceuticals and fine chemicals \cite{10}. The high-production volumes of nanomaterials clearly stress the urgent

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need for developing fundamentally new design of manufacturing methods for nanomaterials that are green and sustainable.

**Emerging strategies for greener routes**

Although still confined to the lab-scale, new synthesis routes that employ sophisticated techniques such as self-assembly, nano-bio interactions, and template synthesis present a great opportunity to address the aforementioned unsustainable nanomaterials manufacturing [11–13]. These new techniques offer high-rate, bottom-up, directed, and precise assembly of molecular building blocks at different length-scale. Most examples of these are conducted in aqueous medium at low temperatures. They involve directed and selective assembly of individual nanomaterials building blocks such that no excess material removal is needed, thereby both reducing waste and the number of required processing steps, and increasing efficiency [14]. If these methods are scalable for industrial production, it is anticipated that they will lower the cost of nanomaterials [12], ensuring long-term sustainability by reducing energy, raw materials, and waste.

Further, it has been also suggested that current and future research should focus on emulating natural designs and eco-design principles as source of inspiration to develop sustainable and scalable processes for manufacturing nanomaterials [9]. For example, diatoms (microalgae) produce nanostructured biosilica, which is achieved by the use of amine functionalised biomolecules [15,16]. These biomolecules play a crucial role in biomineral deposition both as a catalytic agent facilitating the deposition itself and, through their complex self-assembling behaviour at a range of length scales, as a structure director of the resultant inorganic materials. Indeed, the diversity and complexity of diatom frustule morphologies greatly exceeds anything that has been achieved from fully synthetic approaches to date.

Harnessing this biological approach to sophisticated nanomaterials synthesis has exciting prospects for addressing the issues highlighted above of current manufacturing [17,18] because this strategy encompasses most of the twelve principles of green chemistry (see Figure 1) [19]. The synthesis of inorganic nanomaterials using biology has been widely studied. This strategy either employs *in vivo* synthesis (e.g. in microorganisms) or use exotic proteins, enzymes or highly specific biomolecules (either extracted from biomineralising organisms or identified via combinatorial phage display) [20]. Indeed, to date lab-scale green syntheses of ca. 50 inorganic nanomaterials have been reported, which use sophisticated biomolecules. They include metals and alloys, oxides and ceramics, carbonates, sulphides, selenides, arsenides and zeolites (organic materials such as fullerenes, carbon nanotubes, and polymers are also reported) [21–23].

However, bio-based nanomaterials syntheses have significant limitations for industrial uptake, which are mainly associated with prohibitive costs and a limited supply of biomolecules [24,25]. For this reason, great

![Figure 1](image-url)
Focus has been devoted to understand molecular behaviour of biomolecules in search for alternative synthetic analogues that can be available in large quantities at reasonable costs in order to enable large-scale manufacturing of nanomaterials.

**Bioinspired synthetic methods**

Given the limitations of the bio-based methods, a golden mean between synthetic and bio-based methods has been identified. This strategy, dubbed bio-inspiration, involves understanding the chemical principles underpinning the biological routes and then designing synthetic molecules with the desired motifs. Such synthetic molecules help retain the mild, green nature of the biological synthesis while still allowing control of key properties of nano-materials such as particle size, crystallinity and porosity at lab scale [26]. In most cases, these bioinspired processes takes a few minutes, operate at room temperature and in water. These features result in a one-step, mild route using non-hazardous chemicals, with substantial reductions in time and energy usage, yet enabling the synthesis of high-value materials for desired applications.

One application of bioinspired synthesis strategies is in surfactant design as templates for ordered mesoporous materials [27]. We have seen that surfactant-templated synthesis route has revolutionised the field of inorganic porous nanomaterials research since their first report in 1992 [28], however the strategy has ongoing issues in terms of poor resource (raw material) efficiency as the surfactants are often single-use [27,29]. By modifying the chemical structure of these surfactants with bio-inspired motifs [30], renewable surfactants are able to replace the traditional synthetic surfactants, thus reducing the issue of materials intensity in their synthesis (see Figure 2a). Quantitative life-cycle assessments of this improvement remain rare, however one notable example is the synthesis of KIE-6, a glycerol-templated silica material [31]. In that study the authors compare environmental costs for materials produced with pure glycerol and that produced as a by-product in biodiesel synthesis, estimating benefits equivalent to ca. 80% of the heating emissions incurred doing their synthesis. Despite this, the energy costs represented by both synthesis and purification remain high (estimated therein at 3.1 ton CO₂e/ton SiO₂ produced), thus requiring the development of alternative, lower energy processes.

To avert these energy intensity issues in tandem with the materials intensity, a fully synthetic approach using cheaper, fully synthetic molecules, which were entirely inspired from biology (called “additives”) has been developed to establish bioinspired green synthesis [15]. These additives mimic the function of biomolecules that facilitate biomineralisation (see Figure 2bi), thereby enabling synthesis in conditions similar to nature. Initially, such syntheses were limited to systems where the additives (e.g. citric acid or tea extracts) acted as reducing/capping agents in the synthesis of metal nanoparticles where the reaction schemes are straight-forward (e.g. gold and silver) [32].

Recently, researchers have investigated bioinspired synthesis of complex nanomaterials such as metal oxides and ceramics, which follow more complex reaction pathways and include cluster formation, aggregation, self-assembly, polymerisation, etc. [15]These improvements to the synthesis conditions represent a significant [Figure 2](#)

(a) A schematic representation showing bio-based surfactant design (i) combining natural oils/fats with hydrophilic components such as carbohydrates or amino acids. These surfactants self-assemble (ii) into micelles that further template the formation of silica (iii). Upon calcination or solvent reflux (iv), the surfactants can be removed to produce porous silicas. (b) Learning from biomolecules responsible for biological mineral formation (i), synthetic bioinspired additives have been developed, which facilitate the rapid formation of silica under mild conditions (ii). These additives can be removed using conventional methods or a recently developed, room temperature purification (iii), which allows the reuse of the additive, yet producing pure porous silica.
step forward in reducing the barriers for high-volume production, with substantial reductions in time and energy usage (estimated as 2.9 ton CO₂/ton SiO₂ for the materials produced in Ref. [31] compared to 0.23 ton CO₂/ton for bioinspired silica production in Ref. [33]), yet enabling the synthesis of tailored materials for desired applications (see Figure 2bii).

Adoption of bioinspired methods also has advantages beyond the reaction step — one of the largest energy demands for production of surfactant-templated materials lies in the surfactant removal stage of the process [34]. Significant effort has been expended in attempting to avoid this, with effective solvent removal being touted as an excellent alternative to traditional lab-scale calcination [27]. However, refluxing solvents, which is generally required during removal, can actually push the energy intensity of these removal methods above those of calcination [34]. Redesign of the organic molecule has therefore gone a long way towards achieving milder surfactant removal, especially with regards to (bio-)degradable additives [35] or additives with tailored, softer surface interactions to enable milder removal [36—38]. Here, bioinspired additives have been shown to be better for post-synthetic extraction in addition to producing milder synthetics [34]. By taking advantage of biological interactions and motifs, additives have weaker individual binding with the inorganic bioinspired material than fully synthetic alternatives, allowing for easier disruption of the interactions used to synthesise the molecule hence enabling easier extraction and potential reuse of the additives (see Figure 2biii). This engenders large savings in the environmental costs of manufacture — whereas calcination was estimated to produce ca. 0.4 ton CO₂/ton bioinspired silica produced and extraction through ethanol reflux produced ca. 0.9 ton CO₂/ton SiO₂, the aqueous acid elution method developed in Ref. [34] produced only 0.01 ton CO₂/ton SiO₂, a 97% reduction.

Therefore, bioinspired methods can be introduced partially or fully into organic-mediated nanomaterial synthesis to ameliorate a range of issues present within fully synthetic or fully biological systems. Introduction of bioinspired functionality to pre-existing molecules can be used to lower the materials intensity of synthesis, but the best improvements arise from the adoption of newly designed bioinspired additives. These points are illustrated in Table 1 with the example substrate of silica by comparing various well-established silica synthesis approaches, including industrial routes, with a fully bioinspired synthesis method. Although E-factor and specific yields analysis shows little differences between the methods on the face of it, including considerations for reaction and purification solvents clearly demonstrates the material advantage of the bioinspired method in addition to the energy benefits discussed previously. We note that a similar analysis for other nanomaterials is not possible at the moment due to a lack of relevant data. It is hoped that this review, which has identified such gaps, will encourage researchers to focus attention

### Table 1

**Comparison of traditional methods with bioinspired synthesis of silica.**

| Silica type               | Reagentsa | Solvents | Reaction conditions | By-products | E-factorb | Specific yieldc (g.l⁻¹) | Finishing | Control over                  |
|---------------------------|-----------|----------|---------------------|-------------|-----------|------------------------|-----------|------------------------------|
| Mesoporous - MCM-41 [28]  | Silicate, CTAB, ammonia | TEOS, pluronic | Water               | 0.5—168     | 20        | ca. 9 Alcohol, NO₃, CO₂, CO₂, H₂O | Calcination at 550 °C (>6 h) | Pore size, space group |
| Mesoporous - SBA-15 [45]  | Silicate, CTAB, ammonia | TEOS, pluronic | Water               | 12 (60, 900) | 17 (17, 1) | 26 (26, 5, 2) | Calcination or ethanol reflux drying | Pore size, space group, wall thickness |
| Mesoporous – HMS [37]     | TEOS, dodecylamine | Silicate, H₂SO₄ | Water, ethanol      | 18          | 20        | ca. 9 Alcohol, NO₃, CO₂, Na₂SO₄ | 5 (60, 175) | Purity, dispersion |
| Industrial – Precipitated [46] | Silicate, H₂SO₄ | None | Water               | 3–5         | 35–80     | ca. 7 Na₂SO₄ | As above | Sizing, washing, drying |
| Industrial – Fumed [46]    | SiCl₄, H₂O₂ | None | Water               | <0.01       | ca. 400   | N/A HCl | 2.5 | Unknown |
| Colloidal – Stöber [47]    | TEOS and ammonia | Silicate & additive | Water, ethanol | 12—24       | 10–60     | ca. 9 alcohol | 30 (30) | Porosity, purity |
| Bioinspired [15]           | TEOS and ammonia | Silicate & additive | Water             | 0.08        | 20        | 7 NaCl | 38 (38, 13) | dₚ, structure, porosity…d |

a Silicate = Sodium silicate or water glass, CTAB = cetyl trimethylammonium bromide. TEOS = tetraethoxysilane.
b Calculated from representative internal results; numbers in parentheses include reaction solvent, reaction solvent + washing/purification solvent.
c Including ethanol reflux liquid.
d Control over incorporation of foreign material (catalyst, enzymes, drugs, etc.) is also possible.
on both analysing the environmental impact of synthesis routes and inventing new bioinspired synthesis for a wider spectrum of nanomaterials.

Future challenges for bioinspired methods

For bioinspired synthesis to make an impact on nanomaterials production and their commercial use, future research is required to precisely control nanomaterials properties, investigate scale-up and advanced processing (see Figure 3) [3]. Each of these points were discussed during a recent symposium [39], and the key features are highlighted below.

Designing industry relevant materials

Various investigations have reported the observations that additive chemistry, precursor chemistry and chemical conditions strongly influence resulting nanomaterials properties [15,26]. However, the knowledge required for the design of materials, such as the relationship between synthesis-structure-property as well as a full understanding of the kinetics of the process for bioinspired materials is not available. This lack of predictive rules needs to be addressed in order to enable the design of commercially-relevant bespoke nanomaterials using the bioinspired approach.

Scale-up and manufacturing

The bulk of research on bioinspired synthesis has been performed at small scales and, although there are good opportunities for developing nanomaterials manufacturing based on bioinspired approaches, there are no reports on larger-scale investigations for bioinspired methods [40,41].

In order to scale-up for industrial manufacturing, an assessment of cost and availability of resources, scalability and down-stream processing is important. Although biological and bioinspired methods are effective in reducing environmental burden, they might turn out to be expensive, inefficient, and/or not scalable. This can result in
promising new materials technologies not reaching the market owing to issues with producing quantities that are typically required commercially. It is vital to be mindful of these aspects at the discovery and design stage because any alternations to the methods that are required to address scale-up issues are most likely to be easy and cost effective at the discovery stage compared to pilot or industrial scale. To best of our knowledge, such investigations have only started appearing recently and are limited to only one nanomaterial — silica.

Process engineering calculations have shown that green manufacturing based on bioinspired method has the potential for industrial scale implementation [33]. The analysis further highlighted that bioinspired methods for nanomaterials preparation are heavily dominated by the costs of biomolecules/additives [33]. Hence the use of complex biomolecules, in particular those available only in µg-mg quantities, could make the process prohibitively expensive. Where bioextracts are used, due to their scarcity, such methods cannot be implemented on large scales.

In biological and bioinspired methods, the correlations between transport properties, mixing in particular, the reaction timescales and the production scales are unknown (Figure 3), let alone their validation and use in scale-up. There are established methods to assess scalability as well as developing scale-up of processes by understanding the transport properties [42–44]. Further, the downstream processing, e.g. separation and purification of materials, is usually ignored at lab-scales. The downstream separations/purification of nanomaterials formed using these methods are far from trivial. Many of these emerging methods could still potentially suffer from multi-step laborious methods leading to high wastefulness. E-factor analysis shows that purification/separation stages cause large wastefulness due to the excessive use of solvents for washing and the energy required (e.g. centrifugation consume large amount of energy per mass of material separated). Bioinspired methods utilise additives, which remain in the final product as impurities. The downstream purification is highly energy demanding and environmentally damaging [34,38]. As a result, there is a strong need for greener downstream purification (e.g. room temperature additive removal) to produce high-quality, functional porous materials.

Conclusion

Current nanomaterials manufacture is hampered by its environmental wastefulness and associated costs. Bio-based nanomaterials syntheses (in vivo and in vitro) alleviate these issues, however, such methods are impractical for industrial application due to the scarcity of the required biological agents. Bioinspired methods combine the benefits of emerging bio-based methods and existing chemical routes, while avoiding their shortcomings, representing a promising way of marrying current industrial techniques with sophistication observed in nature (Figure 4). To realise this potential, further work on bioinspired methods needs to be focussed on industrial relevance in terms of scalability, economics, materials specifications/properties and compatibility with wider manufacturing techniques, including downstream processing.

Conflict of interest

Nothing declared.

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