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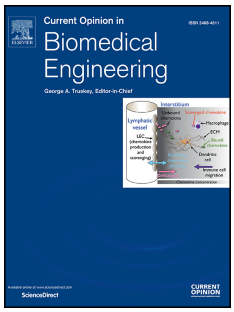

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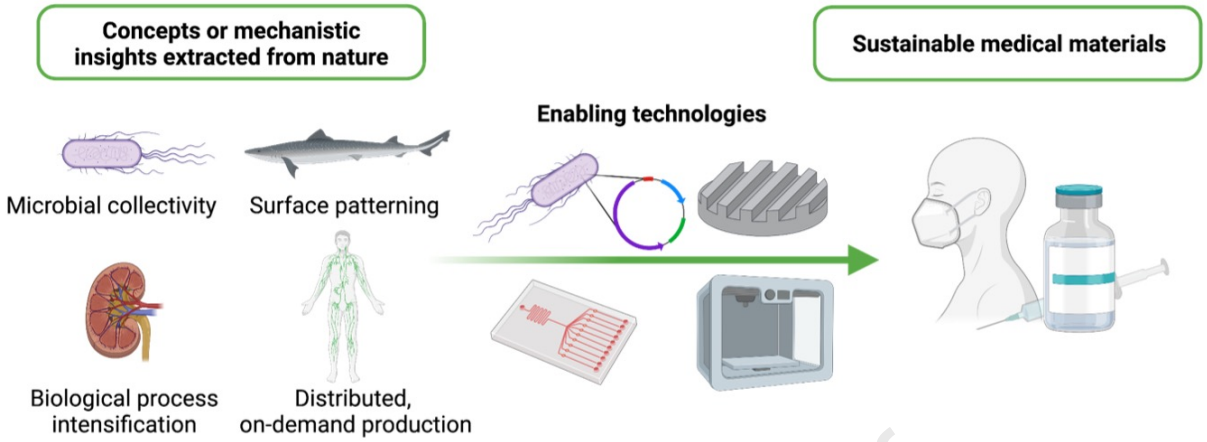
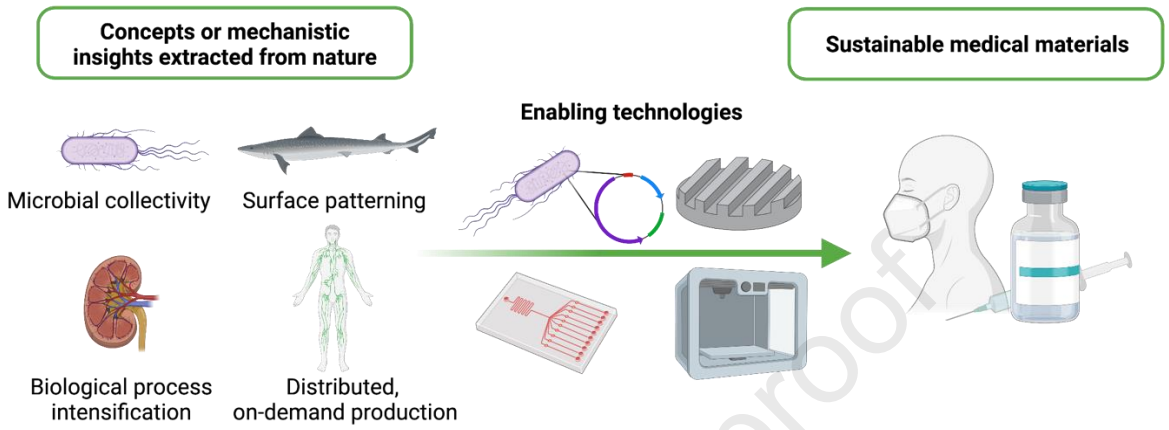


Nature-inspired sustainable medical materials

Matthew H. W. Chin[1], Julia Linke[1] and Marc-Olivier Coppens[1]
[1]Centre for Nature-Inspired Engineering and Department of Chemical Engineering, University College London, Torrington Place, London, WC1E 7JE, United Kingdom

Graphical Abstract



Abstract

As life expectancy increases and health crises arise, our demand for medical materials is higher than ever. There has been, nevertheless, a concomitant increase in the reliance on traditional fabrication and disposal methods, which are environmentally harmful and energy intensive. Therefore, technologies need adaptations to ensure a more sustainable future for medicine. Such technological improvements could be designed by taking inspiration from nature, where the concept of "waste" is virtually non-existent. These nature-inspired solutions can be engineered into the lifecycle of medical materials at different points, from raw materials and fabrication to application and recycling. To achieve this, we present four technological developments as promising enablers – surface patterning, additive manufacturing, microfluidics, and synthetic biology. For each enabler, we discuss how sustainable solutions can be designed based on current understanding of, and ongoing research on, natural systems or concepts, including shark skin, decentralised manufacturing, process intensification, and synthetic biology.

Introduction

Nature presents itself as a sustainable, resource-efficient system where materials are utilised and recycled in a circular fashion. This stands in stark contrast to the paradigm in which humans design, manufacture and dispose of their materials [1–3]. More specifically, medical materials are facing obstacles on the path to integration within a circular economy [4]. Mismanagement of medical wastes poses severe risks to both human health and the environment, as infectious agents and heavy metal pollutants could contaminate surface and ground water. Furthermore, some of the most widely used methods for waste management worldwide are energy-intensive processes, including incineration, that release carcinogens, such as dioxin [5].

The medical waste Issue has been heightened by the COVID-19 pandemic, which – alongside disrupted services and logistics – have led to a dramatic increase in the disposal of personal protective equipment (PPE) and single-use plastics worldwide [6]. The World Health Organisation (WHO) has estimated that, as of December 2021, >140 million COVID-19 test kits have been shipped, with the potential to generate 2,600 tonnes of non-infectious (mainly plastic) waste and 731,000 litres of chemical waste [7]. These numbers are based on shipments through the United Nations procurement system alone. Furthermore, as countries have relaxed restrictions, it is estimated that billions of PPE units will go unused or become unfit for use (e.g., the UK has spent £15bn on unused PPE and other COVID-19-related items) [8,9].

Sustainability necessitates holistic thinking that considers the entire lifecycle, from raw materials and manufacturing to disposal and recycling (**Figure 1**). To achieve this, we can turn to nature for inspiration. In particular, a systematic nature-inspired solutions (NIS) methodology extracts mechanistic principles from processes, functional materials and systems found in nature to apply them in a new setting [10]. This is illustrated via **Error! Reference source not found.**examples discussed in more detail further on: the key mechanism underpinning a remarkable property in nature (source of inspiration), which is also highly desired in the envisioned application, is abstracted (nature-inspired concept) to inform a nature-inspired design that accounts for the different context of the application; this design is prototyped and optimised using experimental and computational tools [10]. The NIS approach can be employed to design a range of healthcare engineering solutions, from drug delivery systems to developmental bioengineering [11,12]. Here, we present how four recent technological developments can be integrated within the NIS methodology to propel the medical materials industry towards sustainability – i) surface patterning, ii) additive manufacturing, iii) microfluidics and iv) synthetic biology.

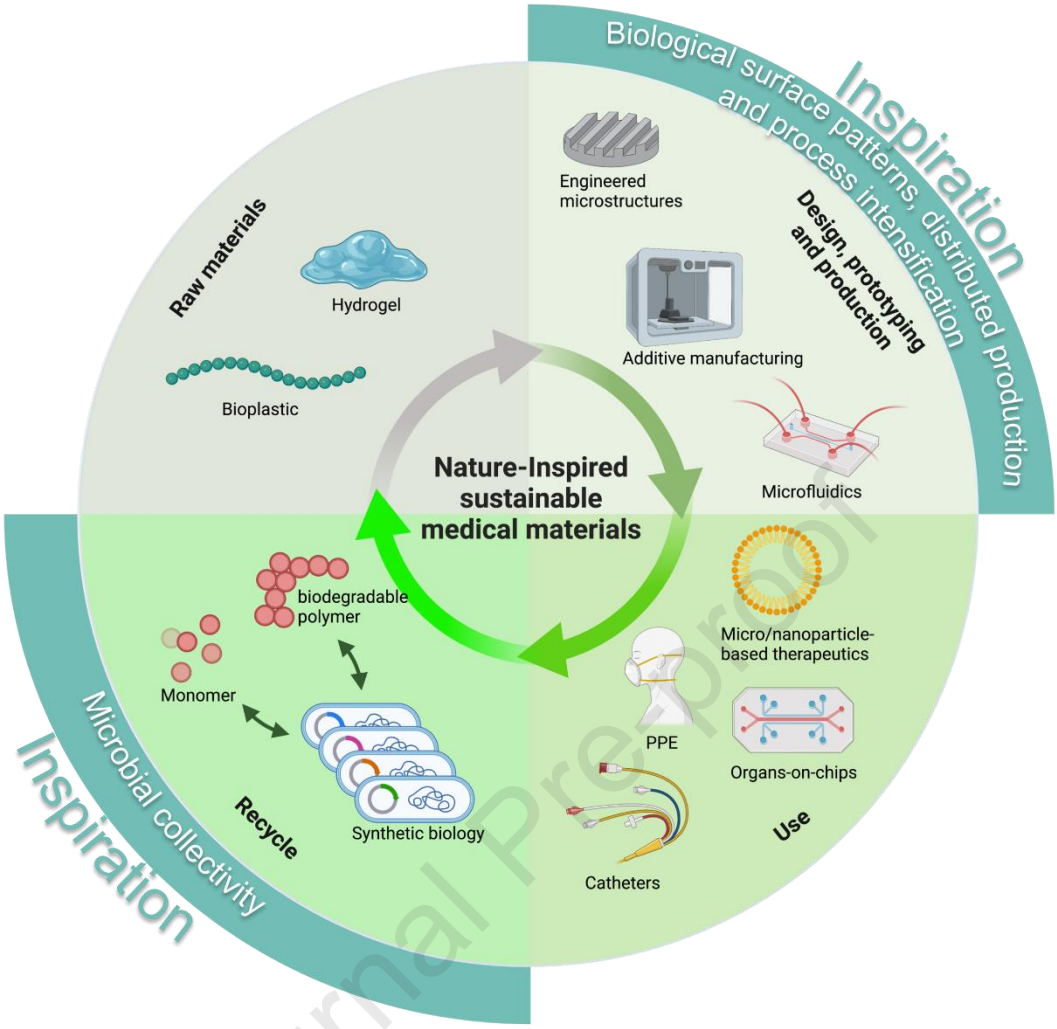


Figure 1. Applying nature-inspired engineering to fabricate and recycle sustainable medical materials. Raw materials, such as bioplastics, can be converted into functional materials or devices using surface micropatterning, additive manufacturing and microfluidics. Inspiration from nature, such as nano- or microstructures present on cicada wings or shark skin, can be leveraged to inform the design of antibacterial/antiviral surfaces for medical instruments and PPE. To enable a more sustainable manufacturing mode, distributed, rather than centralised, production of materials can be used, with optimisation inspired by natural systems (e.g. ant colonies), and implemented via additive manufacturing. The scale of production plants might be reduced using microfluidics to manufacture certain materials, such as particle-based drug carriers. Using parallelised microfluidics, the industrial fabrication of drug carriers could one day be process-intensified in a way similar to that performed by human organs, such as the kidney. Inspiration from physiological systems may also be taken to design organs-on-chips to minimise cost, energy and time in therapeutic development. Completing the cycle, the used materials can be naturally degraded by bacteria and re-synthesised using synthetic biology and the concept of microbial collectivity.

Nature-inspired surface patterning: a sustainable alternative to chemical modification

The functioning of many medical materials relies on physicochemical properties of their surfaces, which often directly interface with the human body. For instance, PPE surfaces act as a physical barrier between pathogens and humans. In addition, surfaces of indwelling medical devices – such as central venous catheters (CVCs) typically used for critically ill patients – need to prevent thrombogenesis, immune activation and resist bacterial colonisation [13]. Thus, surface design is intimately linked to the manufacture and longevity of medical materials, which consequentially influence their sustainability.

Several chemical-based surface modification strategies have been employed in the manufacture of medical tubing to protect humans from infection and thrombotic complications [14]. Widely investigated are perfluorinated liquid-infused, omniphobic coatings [15,16]. Although their cytotoxicity has not been reported as an issue, further studies are required to examine the stability and longevity of the infusing liquid layer under physiological flow conditions [15,17,18]. Moreover, there remain environmental concerns regarding the use of perfluorinated compounds (e.g., the coupling agent, trichloro(1H,1H,2H,2H-perfluorooctyl) silane) to manufacture these materials [19,20].

Structural, rather than chemical, modification is a promising alternative approach that could obviate the use of harmful chemicals and improve the lifetime of medical devices. To this end, there are already well-known examples from nature to draw inspiration from – Arzt *et al.* have provided a comprehensive overview of how biologically inspired micro- and nanostructures can be applied in the realm of medicine [21]. Over the last decade, several nanopillars inspired by insect wings (e.g., cicada) have been demonstrated to possess bactericidal properties (**Figure 2 D-F**) [22,23]. While these experimental studies and biophysical models attributed the cause of bacterial cell death to mechanical rupture and cell lysis, the exact bactericidal mechanism has been a topic of debate. In a recent study, Jenkins *et al*. used scanning electron microscopy (SEM), transmission electron microscopy (TEM) and proteomic analysis to elucidate the mechanisms underlying TiO_2 nanopillar-induced killing of bacteria [24]. It was observed that the nanopillars induced reactive oxygen species (ROS) production and an oxidative stress response in the contacting bacteria. A subsequent study, by Zhao *et al*., demonstrated that mechanical damage caused by nanostructured surfaces could lead to self-accumulating ROS in the injured bacteria and post-stress, apoptosis-like death [25]. With more studies on such multifaceted nature of bactericidal activity, future medical materials could be surface-patterned with nanostructures tailored to specifically induce ROS-mediated cell death in bacteria. In addition, there is potential to apply these surface patterns in a range of medical settings, such as surgical or dental equipment, and on recyclable materials (e.g., the corn starch-based Emteva catheter [26]).

Besides bactericidal effects, surface patterning could prevent biofouling and bacterial colonisation by exploiting the mechanism of force balancing [10]. In biological systems, force balancing occurs at multiple scales, from nano-confinement in transmembrane protein channels to mechanical force balancing in bones. Applying this nature-inspired concept, the geometry of micropatterns may be designed to alter the physicochemical environment of medical material surfaces to impede bacterial adhesion and colonisation. For instance, Shark skin-inspired (Sharklet®) micropatterns have been reported to limit the transmission of pathogens via the proposed mechanisms of hydrophobicity, reduced contact area, and capillary action (**Figure 2 A-C**) [27]. Furthermore, computational fluid dynamics simulations revealed that Sharklet® patterns on reverse osmosis (RO) membrane surfaces could influence biofouling resistance via surface flow characteristics (e.g., vortex streams generated by micropattern protrusions) [28]. However, it remains to be investigated how micropattern geometry, material stiffness and fluid mechanics affect bacterial biology in the context of medical materials. For example, production of signalling molecules, such as cyclic AMP (cAMP), can be triggered in *Pseudomonas aeruginosa* via surface contact [29]. The cAMP can, in turn, stimulate transcription of secretion genes that regulate quorum sensing in biofilm formation. Thus, it would be interesting to study whether nature-inspired micropatterns could be engineered to manipulate bacterial mechanotransduction to inhibit colonisation. In addition, more *in vivo* work on the anti-thrombotic properties of these micropatterns could broaden the medical usage of micropatterns beyond bactericidal applications [30]. Taken together, future developments might lead to optimised micropattern geometries for anti-biofouling in medical devices, including RO membranes in water purification systems for haemodialysis or surfaces in long-term CVCs [30,31].

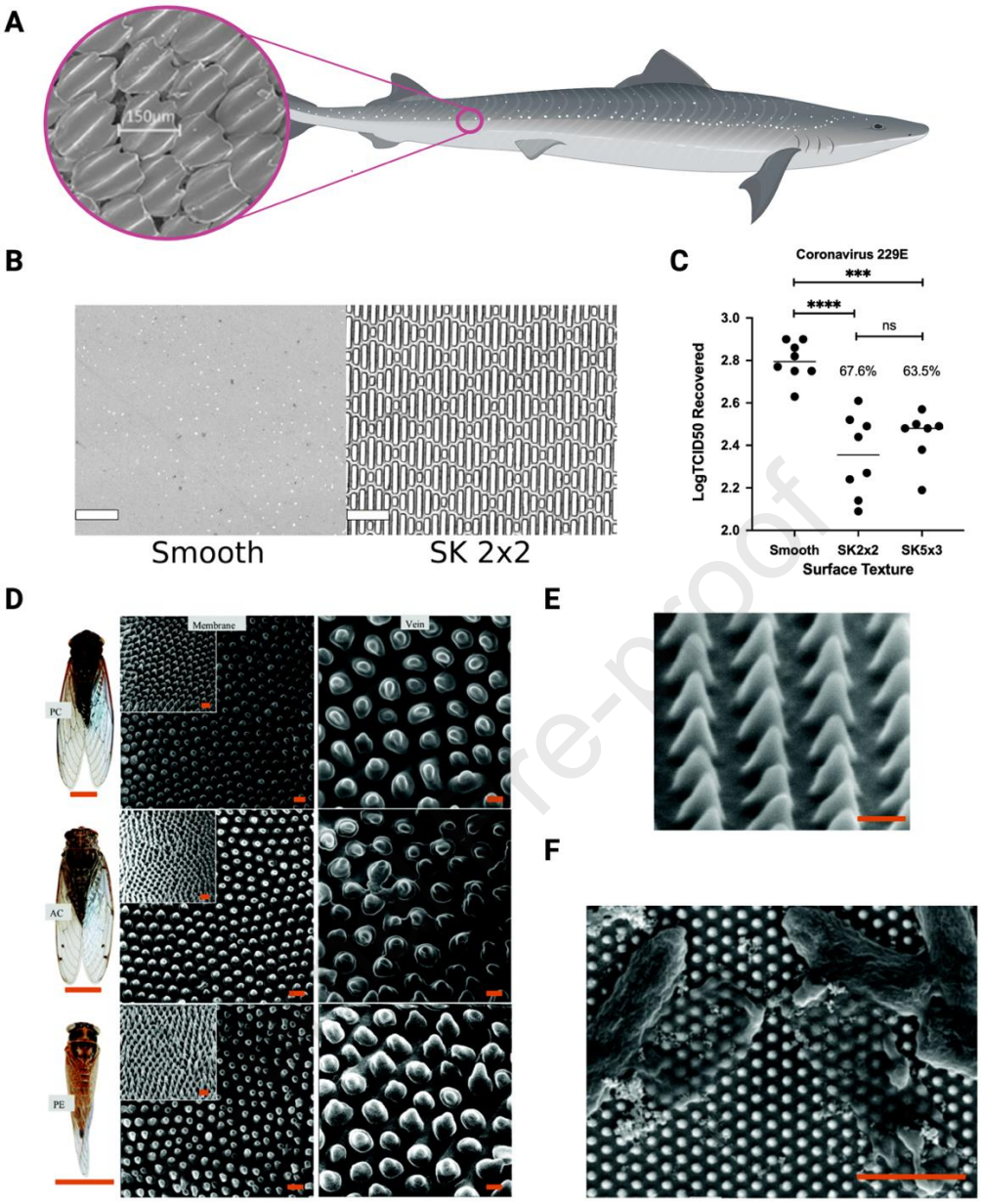


Figure 2. Nature-inspired antimicrobial surface patterning. **A.** Image of shark skin from *Alopias superciliosus* obtained by scanning electron microscopy. **B.** Confocal microscopy images showing smooth and shark skin-inspired micropatterned (SK 2×2) polypropylene surfaces. Scale bar = 20 μm. **C.** Transfer of human coronavirus 229E (a surrogate strain for SARS-CoV-2) to smooth and two variants of micropatterned surfaces (SK 2×2 and SK 5×3). A bead transfer method was employed to simulate touch transfer. The amount of virus transferred was quantified by 50% tissue culture infective dose (TCID50), shown here as log-transformed TCID50 (LogTCID50). **D.** Left column: Cicada species *Psaltoda claripennis* (PC) *Aleeta curvicosta* (AC) and *Palapsalta5yriei* (PE). Scale bar = 1 cm. Middle column: Helium ion microscopy (HIM) images of the corresponding wing membranes with insets showing a 30° tilted view of the nanoscale pillars on wings. Right panel: HIM images of the wing veins of the same species. Scale bar = 200 nm. **E.** Cicada wing-inspired titanium nanopillars fabricated using electron beam lithography (EBL). Scale bar = 100 nm. **F.** *Pseudomonas aeruginosa* bacteria on an EBL nanopatterned surface displaying a disturbed morphology (likely a sign of damaged bacterial membrane). Scale bar = 1 μm. SEM image in **A** was adapted from [32] with permission from Elsevier. Both **B** and **C** were obtained from [27] and reproduced under the Creative Commons Attribution 4.0 licence. Panels **D** – **F** were reproduced or adapted from [33] with permission from with permission from The Royal Society of Chemistry.

Additive manufacturing: enabling decentralised manufacturing of bioinspired medical materials

Many biological and ecological systems exhibit properties of a distributed supply network with flexible manufacturing to allow for adaptivity, speed and efficient resource allocation [34]. Systems ranging from ant colonies to the endocrine system have inspired optimisation algorithms and mathematical models to solve task and resource allocation problems in distributed manufacturing [35,36]. This mode of manufacturing requires enabling technologies not only at the supply chain level, but also the material fabrication level. A rapidly developing technology at the forefront is additive manufacturing (AM) (**Figure 3**). The potential of AM was demonstrated during the COVID-19 pandemic, where 3D printing played a central role in increasing PPE production for hospitals and hospices amidst supply chain disruption [37].

By reducing manufacturing time, energy demand, production waste and shipping distances, 3D printing has the potential to lower the carbon footprint of medical materials [38]. However, there is room for further improvement for AM to be more eco-friendly. For example, acrylonitrile butadiene styrene – a thermoplastic commonly used in making PPE via fused deposition modelling (FDM) 3D printing [39] – is known to give off carcinogenic, volatile organic compounds [38]. Addressing this challenge, polyhydroxyalkanoate (PHA)-synthesising microorganisms may be harnessed to make FDM "green" polymers that are biodegradable and biocompatible [40]. Despite concerns surrounding the cost of PHA (~US$ 10/kg) for biomedical applications [41], advances in synthetic biology (covered in the next section) could address it by enhancing the yield of PHA in the future.

AM is a rapidly emerging field, and we envision that it may enable on-site, (semi-)automated manufacture of the aforementioned, bioinspired, micropatterned medical materials. A prominent technology capable of printing microstructures is two-photon polymerisation [42]. However, mass production of 3D printed micropatterns is limited by the trade-off between printing speed and resolution. Tackling this, there is ongoing development of new technologies, such as femtosecond projection two-photon lithography, which can create sub-micron structures with speeds of 5-20 mm^3/h [43]. Given these promising developments, future efforts can focus on how micropatterned medical materials could be additively manufactured using eco-friendly polymers, such as PHAs.

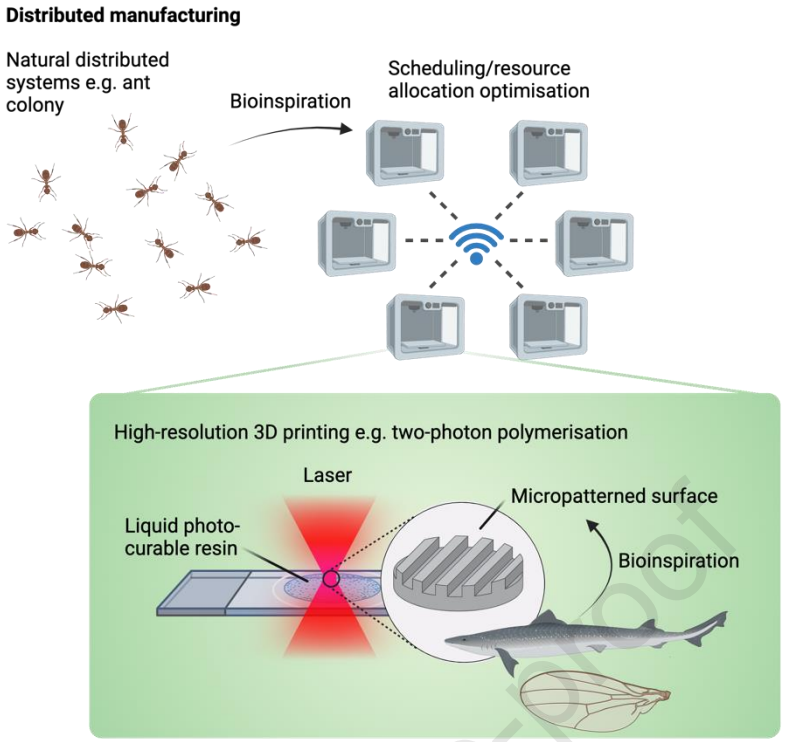


Figure 3. Distributed manufacturing of bioinspired micropatterned surfaces. With advances in high-resolution 3D printing methods, such as two-photon polymerisation, there is now opportunity to additively manufacture antimicrobial surfaces with micropatterns inspired by shark skin or cicada wings. Note that, in a distributed supply chain, the fabrication of a certain product may require different companies to cooperate, which makes the process complex. Therefore, the scheduling within the network, coordination and integration of information could also be optimised for resilience and effectiveness using nature-inspired methods, such as ant colony optimisation.

Microfluidics: intensification of medical material manufacturing

As illustrated with the AM example, decentralisation of manufacturing brings forward the idea of having small-scale production plants distributed across many locations. This approach could minimise the environmental footprint of not only protective medical materials, but also therapeutic materials, such as vaccines [44]. However, questions remain how small-scale facilities can meet the high-throughput production rates typically associated with centralised production (**Figure 4**). Here, we highlight how recent advances in the field of microfluidics present a pathway for process intensification, where distributed, small-scale manufacturing can be implemented without compromising production rates.

Microfluidics can be used for fabricating a range of bioinspired medical materials – a prominent example being drug carriers created by microfluidic droplet generators, such as macrophage-inspired nanovesicles [45] and octopus-inspired, suction-cup-like microparticles [46]. Compared to conventional particle synthesis, the microfluidic route is attractive because of advantages including enhanced drug yield and reduced burst release of the drug [48]. However, microfluidics has often been criticised for having low production rates. This stands in contrast to how processes are intensified within biological organs that take up only a small footprint. For instance, the human kidney, while having a volume of just ~150-200 mL, can pack ~1 million filtering units (nephrons) [47,48]. Tackling this challenge, Yadavali *et al.* managed to create a very large-scale droplet integration (VLSDI) platform with >10,000 microfluidic droplet generators [49]. The parallelised microfluidic architecture of the VLSDI was designed by tuning relative fluidic resistances (between the droplet generators and distribution channel) to maximise the production rate of uniform particles,

while incorporating the largest number of droplet generators on the same silicon wafer. Using the VLSDI platform, the authors demonstrated a production rate of 328 billion polycaprolactone particles (a biodegradable and biocompatible material) per hour. With this performance, the authors estimated that for HIV patients undergoing anti-retroviral therapy (in the form of microparticle-based injectables), <100 chips continuously running 24 h a day could provide the world's supply. More recently, Shepherd *et al.* used a similar design to manufacture lipid nanoparticles (LNPs) for encapsulating RNA therapeutics [50]. This work has therefore demonstrated the potential for a scalable and point-of-care approach to manufacture LNP-based RNA vaccines, which have played a major role during the COVID-19 pandemic and will likely remain crucial in combating future novel pathogens.

Besides manufacturing therapeutics, microfluidics can shorten the overall research and development cycle of medical materials via animal-free, low-volume experiments that minimise laboratory waste and energy consumption [51]. In particular, organs-on-chips (OoCs) are microfluidic devices that recapitulate physiologically relevant microenvironments *ex vivo* to simulate pathological conditions and test therapeutics [52]. Successful examples where OoCs produced more accurate, predictive results than animal models already exist [53] – e.g., in the prediction of drug-induced hematotoxicities [54] or hepatotoxicities [55]. Nevertheless, creating increasingly complex microenvironments (or combinations of different microenvironments in body-on-chips) remains a challenge [53]. The lack of regulatory standards has also made its adoption by pharmaceutical companies difficult [56]. To overcome these obstacles, a sound, mechanistic understanding of complex physiological systems would be required. Employing the NIS methodology, we might, for instance, take inspiration from the spatial relationships between cells in different organs, as well as tissue mechanics, to design the next generation of OoCs. These insights could be translated in the future to create structurally complex microenvironments via 3D bioprinting to precisely position cells and control tissue mechanics within OoCs [57]. To this end, 3D biofabricated constructs (e.g. cell-laden hydrogels) are a promising alternative to synthetic plastics, as the former could more closely recapitulate the mechanical, architectural and physicochemical properties of living tissues [58].

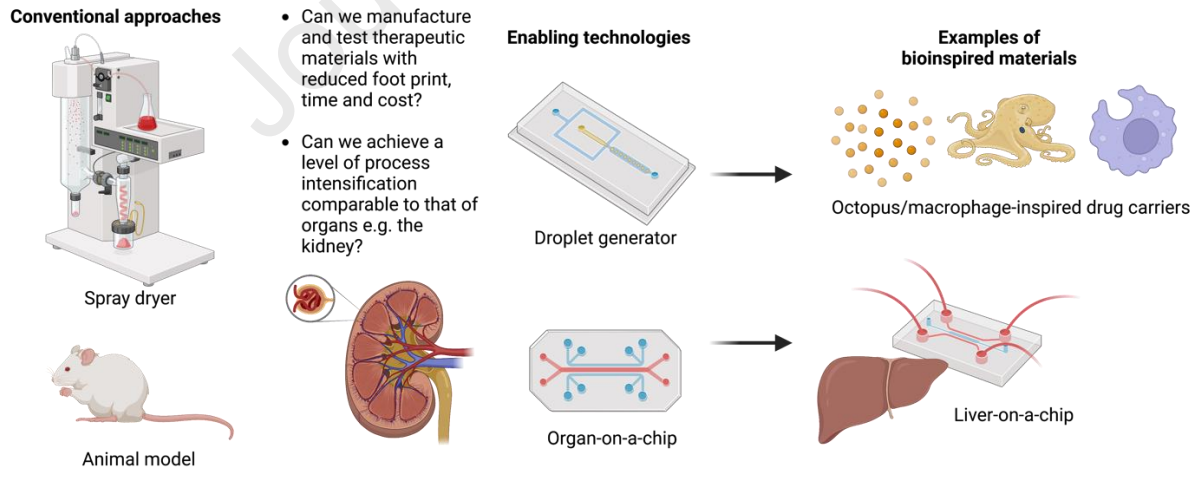


Figure 4. Microfluidics presents a pathway towards intensification of therapeutic production and testing. Microfluidic droplet generators can outperform conventional approaches (e.g., spray drying) of manufacturing particle-based drug carriers, in terms of particle uniformity and drug yield. The high-precision control of microfluidics also enables the application of nature-inspired engineering to endow particles with advanced drug-delivery properties. Furthermore, organs-on-chips, by exploiting the principle of organogenesis, can recapitulate various physiological environments and mitigate the use of unreliable and costly animal models.

Using synthetic biology for nature-inspired material circularity

Petrochemical-based plastics are used in a broad range of medical applications, from medical devices and disposable syringes to gloves and packaging. For sustainability, there is a desire to explore renewable biomass as an alternative to petrochemicals in the production of plastic materials [59]. Tackling this challenge, solutions may be designed based on nature's strategies to achieve circularity of materials – a well-known approach is the ability of bacteria to metabolise and reuse organic matter.

Bacteria, such as *Ralstonia eutropha*, are well-known for their ability to synthesise PHA (e.g., polyhydroxybytyrate, PHB) as carbon storage molecules during times of nutrient limitation and carbon excess [60]. The biodegradability and biocompatibility of PHA make its polymers particularly attractive for applications such as bioresorbable surgical sutures, implants, and drug delivery [61]. Through synthetic biology and metabolic engineering, *R. eutropha* or recombinant *Escherichia coli* harbouring biosynthesis genes (the phaCAB operon) have been employed as "living factories" for PHA production [62]. For circular production, there is also active research in the field to harness bacteria, such as *Paraburkholderia sacchari*, to convert PHA degradation monomers back into PHA [63]. Yet, the economic competitiveness of PHA has been limited by its production costs, which are currently higher than those of petrochemical plastics [62].

The high costs stem from the complicated bioprocessing involving energy-intensive sterilisation, low carbon-PHA conversion, and complex downstream separation. Addressing this challenge, the possibility has been explored to produce PHA using extremophilic bacterial strains, such as *Halomonus* spp., a family of halophilic (salt-loving) and alkaliphilic gram-negative bacteria. Using this approach, contamination-free PHA production can become possible under open, unsterile conditions at high salt concentrations and high pH [64].

In a more recent effort to improve PHA production, Kratzl *et al.* took inspiration from the division of labour among specialised microbes to intensify PHA synthesis in a "one-pot" fashion [65]. In nature, microbes often exist in consortia consisting of many different species – this often establishes networks of advantageous interactions benefitting the survival of the collective (e.g., increased resistance or joint conversion of metabolites). This concept of microbial collectivity was turned into a rationally designed co-cultivation system involving *Pseudomonas putida* and *Synechococcus elongatus cscB* to produce PHA from light and CO_2. Here, *S. elongatus cscB* is a photosynthetic cyanobacterial strain that has been engineered, with an *E. coli*-derived *cscB* gene, to secrete sucrose. The sucrose, in turn, acts as a carbon source for the co-culture partner, *P. putida* that was genetically modified to metabolise sucrose for PHA synthesis. *P. putida* provides CO_2 and limits O_2 accumulation for the phototroph. This "one-pot" system directly converts cyanobacterial feedstock into PHA, which mitigates the cost of sugar recovery form the fermentation broth and the use of crop-based feedstock. Furthermore, the authors used a mathematical model to predict the feeding rate of urea as a nitrogen source required to optimise the carbon-to-nitrogen concentration ratio in the culture medium, which is known to influence PHA accumulation in bacteria.

Looking ahead, an emerging area where PHA may serve as a promising sustainable material is tissue engineering. For instance, PHB can be mixed with hydroxyapatite (HA) and alginate (ALG) hydrogel to form composite scaffolds via a combination of indirect 3D printing and salt leaching [66]. Mesenchymal stem cells (MSCs) seeded on the PHB-HA-ALG scaffold *in vitro* were shown to undergo osteogenic differentiation. Moreover, the MSC-seeded scaffold demonstrated *in vivo* osteoinductive activity by stimulating regeneration in parietal bone defects in rats. Taken together, a nature-inspired approach has the potential to synergise with synthetic biology to drive the manufacturing of future biopolymer-based materials (**Figure 5**).

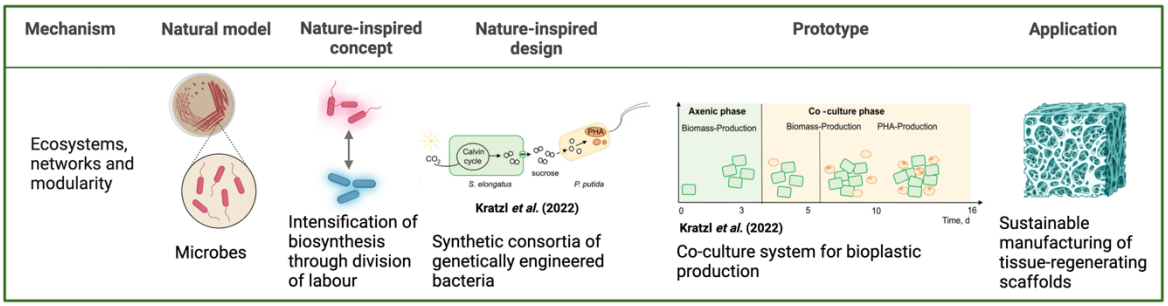


Figure 5. An example illustrating application of the NIS methodology in the context of medical material production. Within chemical engineering, the NIS methodology has been developed into an approach known as nature-inspired chemical engineering (NICE), which exploits mechanisms found in nature to solve problems in a different context. This approach may be applied to sustainable medical materials, as exemplified by Kratzl *et al.* in their work [65], which relates to ecosystems, networks and modularity [10]. Figures under "Nature-inspired design" and "Prototype" were reproduced under the Creative Commons Attribution 4.0 licence.

Conclusions

To achieve sustainable circularity for medical materials, innovative technologies are required for their fabrication and reuse. An opportunity to develop such technologies is to draw inspiration from nature, which exemplifies circularity beyond current human recycling efforts – which are, furthermore, mostly absent for medical materials. However, to be effective, learning from nature requires a methodology to systematise the development from nature-inspired concept to design and to implementation. Such a methodology is offered by the NIS framework. Here, we have identified surface patterning, additive manufacturing, microfluidics, and synthetic biology as rapidly developing fields and technological enablers to be employed within the NIS framework. We envision that, in the future, synthetic biology could drive the synthesis or degradation of polymeric materials for the manufacture of medical materials in a distributed manner. This mode of manufacturing would be enabled by networks of 3D printing facilities, with capabilities to instil materials with bioinspired, antimicrobial properties via surface patterning, rather than chemical modification. Besides creating PPE and medical equipment, microfluidics could also be employed to produce and test therapeutic materials in a high-throughput, reliable and cost-effective manner. Given recent developments of these fields, the NIS framework offers a chance for accelerated innovation of medical products that are fabricated and distributed in a "green" manner, using biosynthesised materials, with minimal need for energy-intensive processes or environmentally harmful chemicals.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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