to competitor or predator species. Through the introduction of seawater as the main medium and a splash of wastewater to nourish the algae, the development of this promising factory could also contribute to preserving freshwater resources and recycling chemical nutrients in wastewater.

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Forum

Bionic Manufacturing: Towards Cyborg Cells and Sentient Microbots

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Bio-inspired engineering applies biological design principles towards developing engineering solutions but is not practical as a manufacturing paradigm. We advocate 'bionic manufacturing', a synergistic fusion of biotic and abiotic components, to transition away from bio-inspiration toward bio-augmentation to address current limitations in bio-inspired manufacturing.

> "We can rebuild him. We have the technology. We can make him better than he was. Better, stronger, faster (*The Six Million Dollar Man*, 1973, a television series based on *Cyborg* by Martin Caidin, 1972)".

Genesis of Bionics: Transcending Biogenics and Biomimetics

The word 'bionic' conjures fascinating images of futuristic beings that comprise biological and mechanical components. At least, this is the interpretation that has inspired countless works of science fiction over the past half-century. However, when Jack E. Steele originally coined the term he was promulgating a new scientific paradigm based on the application of biological design principles toward the development of engineering solutions for addressing technological needs [1]. Steele would undoubtedly be pleased were he to survey the grand body of work that is now catalogued as bio-inspired engineering or biomimetics, particularly the long list of advanced functional materials that are now routinely employed in biomedical applications. While biogenic materials are essentially designed by incorporating biological extracts (from plants, microbes, or mammalian cells), bio-inspired materials imitate or mimic biological phenomenon (such as gecko-mimicking surfaces, mussel-inspired adhesives, etc.) by imparting similar physicochemical properties. However, the absence of biogenic or biotic components in bio-inspired materials limits the range of their properties and applications. This is not only evident in biomedical applications but also in manufacturing, where regeneration and responsiveness to process stimuli are essential for sustaining productivity. This transcendence of biogenics and biomimetics can be clearly seen in the development of medical-grade biomaterials where the first generation of biomaterials focused on bio-inertness (e.g., wood), the second generation was about bioactivity, and the third generation transitioned to bio-regeneration (Figure 1). Possibly, the fourth generation could involve not only fusing biotic and abiotic components together but also their innate regeneration/transfer of 'improvised' traits in the future (so-called 'bionic superiority'). This concept is similar to heterosis or hybrid vigor, in which an offspring exhibits enhanced traits as a result of mixing the genetic contributions of its parents. In this case, improvised/novel traits appear owing to the synergistic fusion of biotic and abiotic components.

We propose developing a new class of biotic systems for use in manufacturing by seamlessly fusing living and non-living materials together. We refer to these hybrid systems as 'bionic systems' (or 'bionic microsystems' based upon their size), and to the new manufacturing paradigm as 'bionic manufacturing' (as highlighted in Figure 1). In addition, while several reviews have already been written on biomedical applications of such hybrids, our discussion will be focused on a novel and largely untouched area of bionic manufacturing – that of their use as next-generation cell factories, bionic micromotors, and applications thereof. To this end, we also posit that bionic manufacturing could be the solution to our energy and material needs.

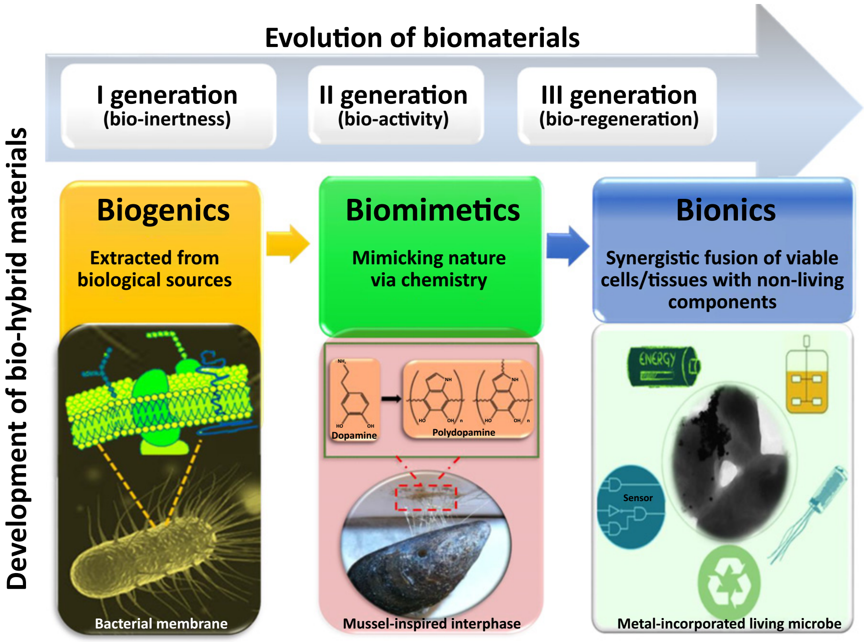

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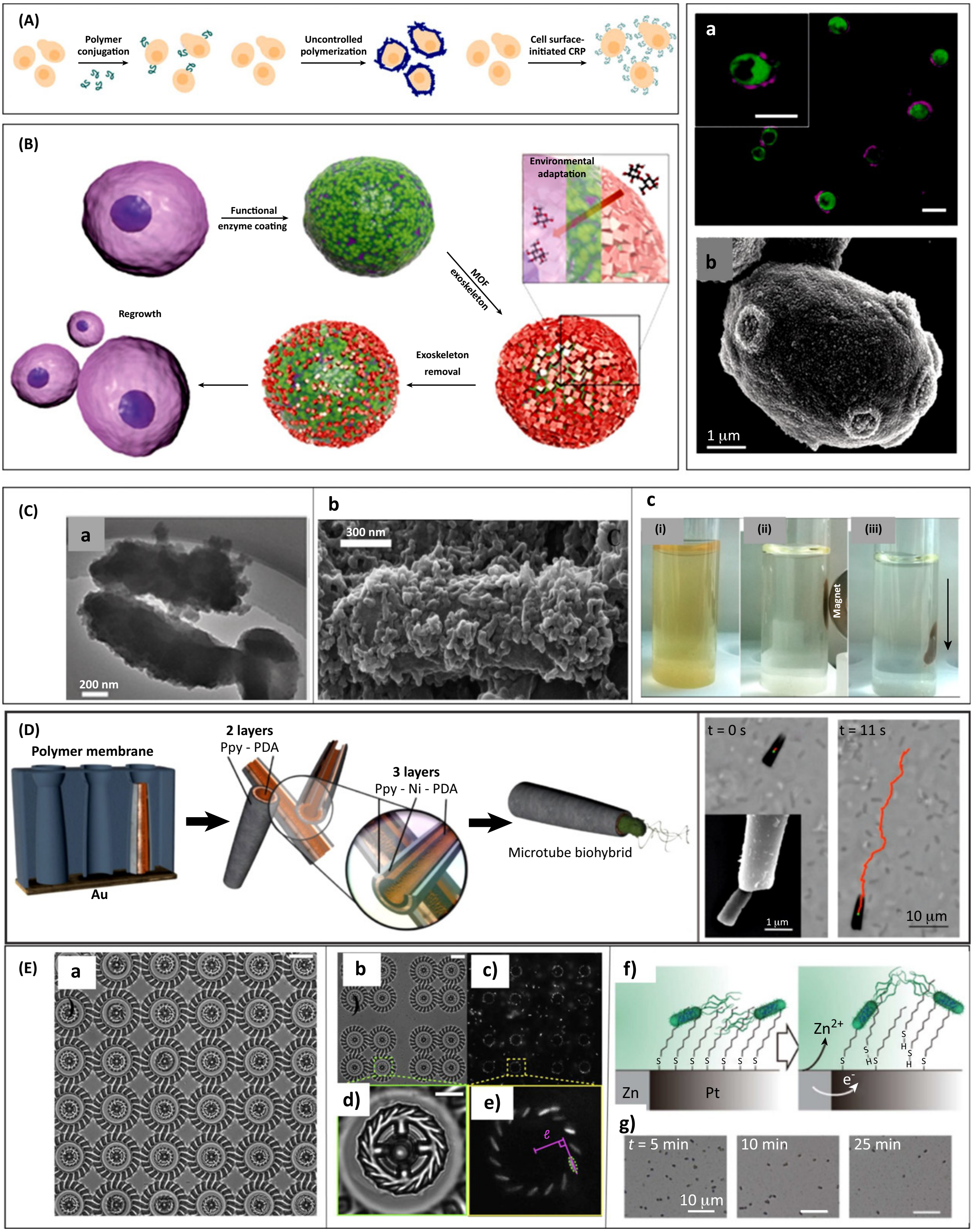
Figure 1. Trends in Bio-Based Material Design and the Onset of Bionic Manufacturing (with Graphically Illustrative Examples).

Cyborg Cells and Sentient Microbots for Manufacturing and Sustainability

Bionic cells or 'cyborg cells' can be produced either by functionalizing microbial or any other biosynthetic host cells with nanoparticles, or by coating the cells with polyelectrolytes or forming hard shells on the cellular surface through polymer-assisted assembly of nanomaterials [2]. This process should not be confused with *de novo* synthesis of living cells/cellular organelles, at least not at its current stage. Likewise, the term 'sentient' generally refers to responsiveness or perception of a living entity. Both eukaryotic and prokaryotic cells exhibit remarkable levels of 'awareness', often described as 'taxis' (durotaxis, chemotaxis, gravitaxis, and so on).

For example, Hawker and colleagues [3] coated the surfaces of microbial and mammalian cells with functional polymers via cytocompatible, controlled polymerization to facilitate the manipulation and selection of desired cellular phenotypes (Figure 2Aa). Likewise, Zhang and colleagues [4] coated cells of *S. oneidensis* MR-1/CC with a conjugated polymer, polypyrrole, and observed that electron transfer and cellular viability of the cells improve considerably when they are cultured in a microbial fuel cell (Figure 2Ca). In fact, the power density of the fuel cells improves 14-fold on average when the bionic *S. oneidensis* cells are employed in lieu of the wild-type strain, which underscores the fact that functionalizing the cellular surface of exoelectrogenic bacteria greatly improves the performance of the microbial fuel cells that harbor these strains. In another study, Konnova and colleagues [5] functionalized cells of *A. borkumensis* with magnetic nanoparticles (Figure 2Cb) and demonstrated magnetically facilitated cell displacement on an agar substrate (Figure 2Cc). The bacterial cells are covered with 70–100 nm magnetite shells, which were removed naturally after multiple cell proliferations. Strikingly, however, when the bacterial cells are transformed with the magnetosome or similar metal-sequestering genes [6], their magnetic trait becomes inheritable. Because magnetized microbial cell factories can be easily purified from the fermentation broth using magnetic beads, the use of these systems in continuous biomanufacturing is especially enticing. Similarly, sentient microbots with micromotor technology have been extensively studied for biomedical applications. However, these bionic systems can be easily extrapolated towards bio-manufacturing, environmental sensing, and remediation.

Stanton and colleagues [7] achieved a similar objective using a different strategy. They appended magnetically actuated microtubular structures onto *E. coli* (Figure 2D). The microtubes were synthesized by coating a bacteria-attractant polydopamine inner layer with magnetic particles and the *E. coli*. Such a bionic microbot design may have an advantage over single-component systems such as genetically engineered bacteria or catalytically powered micromotors/pumps, and needs to be further investigated. This modification nonetheless has interesting possibilities for the manufacturing of value-added products, as was recently demonstrated by one of us in a first-of-



Trends in Biotechnology

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its-kind study [8] towards rapid synthesis and purification of vanillyl alcohol.

In addition, Di Leonardo and colleagues [9] successfully fabricated bacteria incorporating microgears that demonstrated photocatalyzed chemotaxis (Figure 2Ea–e). Their fabrication strategy trapped bacterial cells in a 3D-printed microrotor setup. The bacteria were genetically engineered to express the light-driven proton pump, proteorhodopsin, and the micromotor generates stable and highly reproducible torque. In similar vein, Yoshizumi and colleagues [10] employed a Zn/Pt-based micromotor as the basis for transporting *E. coli* (Figure 2Efg) via hydrophobic interactions exploiting the redox potential difference of the micromotor setup. Bionic micromotors (which are also known as bio-micromotors or biohybrid microbots) may offer substantial benefits that need to be investigated further by the scientific community (and in particular, the nano/micromotors community), a few of which include (i) the recovery of precious metals lost through bioleaching and bioaccumulation [11], and (ii) environmental sensing and bioremediation: micromotor-coupled bionic cells can easily be activated via native or induced genetic pathways in the presence of a target pollutant, and combine biodegradation with autonomous propulsion, thereby serving as next-generation environmental monitoring and remediation systems. These bionic microsystems can be easily deactivated via the incorporation of a 'kill switch' upon clearing the target pollutant [12]. Furthermore, (iii) bionic microsystems for sensing (bio-electronics) and reporting metabolic processing and cell culture conditions permit online monitoring and dynamic control of bioprocesses, as demonstrated by Zhou and colleagues [13]. In their study the team combined motile bacteria with lyotropic liquid crystals that respond to stimuli such as oxygen content, metabolite concentrations, temperature, and pH.

Bionic Systems: Challenges and Opportunities

Although bionic manufacturing is still at a nascent stage, it clearly has enormous potential in manufacturing, clean energy, and sensing. Nevertheless, some challenges need to be addressed to make it broadly applicable, the most crucial being preservation of cellular viability during operation. To this end, a recent study offers a potential solution. Liang and colleagues [14] coated yeast cells with a metal–organic framework (MOF) that itself is enveloped by a β-galactosidase/ZIF-8 exoskeleton (Figure 2Bb). The resulting shell is bioactive and serves as a protective shield that also selectively enhances the transport of nutrients to the cells. The coating greatly improves cellular viability in adverse environments including toxic agents (for environmental remediation of toxic waste) and UV irradiation (toward photoactuation of nano/microbots). As of now, there exist two main challenges for bionic systems (i) extending the viability and lifespan of a bionic cell/microbot setup, and (ii) achieving greater control over the interaction between the biotic and abiotic components. Possible solutions should improve biotic and abiotic components within the system. For instance, targeted genome engineering using CRISPR/Cas9 can be utilized to introduce genome-wide modifications in the host cell so as to make them sturdier under industrial/operational conditions [15]. Further, the issue of cellular viability can be addressed by deploying a 'feedback mechanism' or biogenic design scheme wherein the bionic system is fabricated via the activity of the living cell and bio-augmentation. This is crucial for a bionic system because it should exhibit both fusion between a living cell and an abiotic architecture for acquiring novel traits or enhanced performance, and maintain the biotic components (such as cells) in a viable state.

The Future: Better, Stronger, Faster

These bionic systems not only offer new insight into how traditional problems in industrial biotechnology can be approached but also offer investigative tools for single-cell and consortial biology. Although this highly multidisciplinary area of research is evolving rapidly (including design and applications), much more still needs to be understood about the

Figure 2. Applications of Bionics. (A) Cytocompatible polymerization and associated image of a polymerized cell (a) highlighting a living cell (green) and the polymeric coat around it (purple). Abbreviation: CRP, controlled radical polymerization. Image reproduced, with permission, from [3]. (B) Fabrication strategy for a biocompatible metal–organic framework (MOF) shell comprising β-galactosidase/ZIF-8 around yeast cells: (b) scanning electron microscopy (SEM) image of the resulting cell@shell morphology (core-shell structure). Image reproduced, with permission, from [14]. (C) Coating of *S. oneidensis* cells MR-1/CC with polypyrrole (Ppy) polymer (a) towards microbial fuel cell application. Image reproduced, with permission, from [4]; (b) SEM image of magnetically modified *A. borkumensis* bacteria; (c) magnetically modified *A. borkumensis* cells acquire magnetic responsiveness. (i,ii) Targeted movement of magnetic cells facilitated by external magnetic field (in liquid media); (iii) sedimentation of magnetically concentrated cells. Image reproduced, with permission, from [5]. (D) Bacteria-driven microtubular microswimmer concept via Ppy–Ni–polydopamine (PDA)-incorporated microtubes. Tubes were released from scaffold and incubated with *E. coli* to create a biohybrid microswimmer and associated motion trajectory. The inset displays a SEM image of the microtube swimmer with the attached bacterium. Image reproduced, with permission, from [7]. (E) Bright-field microscopy image of (a) 36 rotating micromotors (scale bar, 20 μm); (b,c) array of 16 rotors used to characterize the rotational dynamics; cell bodies are clearly visible in fluorescence. (d,e) Zoomed view on one of the rotors in (b,c). Cell bodies are fitted with an ellipsoidal shape shown as a dashed line in (e). Image reproduced, with permission, from [9]. (f) Autonomous release of *E. coli* from a Zn/Pt self-assembled monolayer (SAM) composite electrode. (Left) Adhesion of *E. coli* to the SAM. (Right) Reductive desorption of alkanethiolates taking place simultaneously with the dissolution of zinc, releasing *E. coli* cells from the electrode. (g) Time-lapse microscopy images during the release of *E. coli* cells. Image reproduced, with permission, from [10].

principles that govern the interactions between biotic and abiotic components. The next decade promises to be an exciting time for the field, and we expect numerous strategies and applications to emerge. Some, optimistically, will be translated to industry. The future of bionics, as foretold by Martin Caidin, indeed promises to be 'better, stronger, faster'.

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