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ScienceDirect

Current Opinion in
Biomedical Engineering

Current developments in multifunctional smart materials for 3D/4D bioprinting

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Tissue engineering and regenerative medicine (TE&RM) has made continuous advancements by extending three-dimensional (3D) printing towards the development and fabrication of biomimetic scaffolds composed of biomimetic natural and synthetic materials. Although several clinical applications of 3D-printed scaffolds made of classical biomaterials have yielded promising results, current basic research trends have shifted towards rendering scaffolds "smart" or dynamically responsive where shape changes are induced by external stimulation (ie. electromagnetic radiation, mechanical stress, heat) or physiological changes in the local microenvironment through pre-designed mechanisms of action. Although a bulk of the research efforts have led to high-impact publications demonstrating the capabilities of these technologies, hardly any studies have been published illustrating the application of these research efforts in a clinical context. Herein, we will discuss current trends and advancements of 3D printable bioinks and highlight the most recent developments (2015-present) of 3D-printed smart materials also commonly referred to as 4D printing/programmable matter. We will conclude with a prospective opinion of this research field where innovation is synonymous with risk-taking. High-risk, high-reward research founded on revolutionary innovations are often disruptive and lead to new paradigms; conclusively the 4D printing can be disruptive, because it has the potential to change the current paradigm by changing the question from "what can we do with these materials/technologies?" to "how can we move the concept/technology forward to achieve what we need".

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Current Opinion in Biomedical Engineering 2017, **2**:67–75

This review comes from a themed issue on **Additive Manufacturing**

Edited by **Seeram Ramakrishna, Carlijn V. C. Bouten and Roger Narayan**

http://dx.doi.org/10.1016/j.cobme.2017.04.002

Keywords
4D printing, Programmable matter, Gelatin methacryloyl (GelMA), Bioink, Smart materials.

Introduction

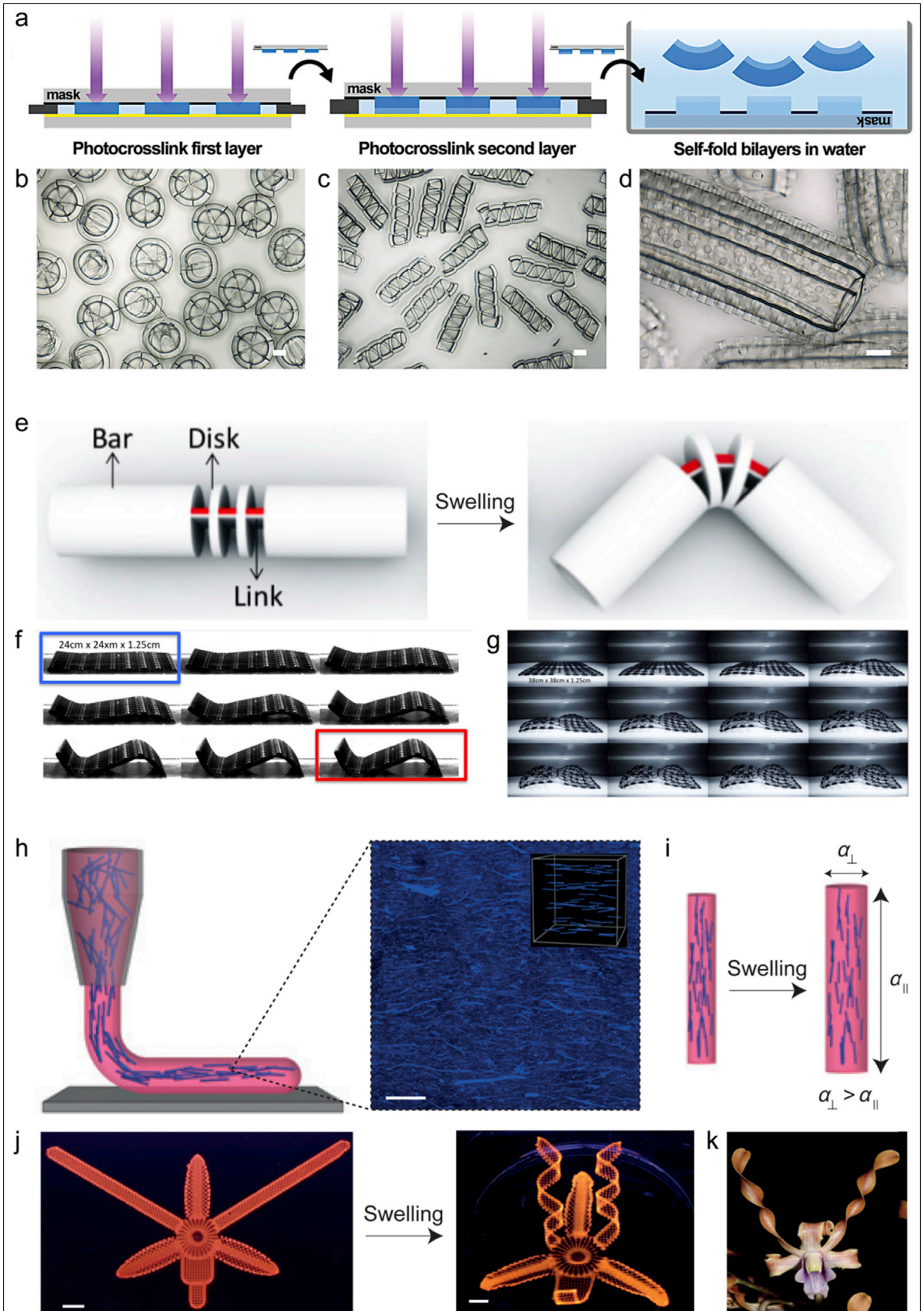
The rise in four-dimensional (4D) printing can largely be attributed to a widely broadcast 2013 TED (Technology, Entertainment, Design LLC, a non-profit company devoted to idea dissemination) talk in which shape-changing 3D printed structures were presented [1–3]. Since that day, the concept of 4D printing has rapidly developed and expanded its breadth and depth leading to an increase of high-impact original research introducing novel manufacturing approaches/materials. Unfortunately, few follow-up publications have extended the understanding of these materials in depth or evaluated reproducibility and up-scaling on these techniques and approaches.

Dynamic shape changing materials are typically fabricated by multi-material 3D printing techniques, but the definition of "4D printing" has quickly become ambiguous and broad. As a result, a more detailed definition specifically stating the constraint of requiring shape or functional change be inducible directly after printing. Other criteria have also been established as reported by The Atlantic Council of the United States where 4D printing is defined as: 3D printing of objects which can self-transform in form or function when exposed to a predetermined stimulus, including osmotic pressure, heat, current, ultraviolet light, or other energy sources [4–6]. Even so acclaimed by the early publications it needs to be shown if the technology holds great potential in a myriad of industries and applications including TE&RM. Hence, in the following we will critically review, highlight and discuss novel programmable matter formulations and 3D printing strategies in the context of what is defined as bioprinting for potential use in TE&RM.

Osmotic pressure-driven hydrogel-based bioinks

A simple mechanism facilitating 4D temporal shape transformation of 3D printed materials is the utilization of the intrinsic swelling characteristics of hydrogels. A pioneering example demonstrating this fundamental

Figure 1



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