regulatory definitions to clarify whether all forms of genome editing [site-directed nucleases 1–3 (SDN1–3); see Table II in Box 1] fall under the existing GE/GM regulatory framework. Alternatively, some jurisdictions regulate GE/GM and genome-edited organisms according to a product trigger (e.g., Canada and USA), under which the relevant novelty of the trait in question was considered on a case-by-case basis, irrespective of the technology used to develop it. Finally, some jurisdictions had already passed resolutions on the regulation of new (plant) breeding techniques [N(P)BTs], including the subcategory of genome editing (e.g., Argentina).

Those jurisdictions that have already regulated and allowed genome-edited products on the market reported a noteworthy statistical change in the nature of applicants: while traditional GE/GM dossiers had predominantly been submitted by (foreign) large multinational companies, most genome-editing applications originated from (local) public research institutions and small and medium-sized enterprises.

The regulatory session concluded that more effort was needed from all stakeholders to improve and prioritise both the communication and the information exchange concerning genome editing to ultimately create a market for the beneficial products resulting from such technology: public risk communication by both advocates and opponents needed to be fact and science based, without overburdening the nonspecialist public with undue information.

> [In] the last 25 years, we have been collecting more and more and more data and demonstrably not improved public confidence (OECD Conference on Genome Editing: Applications in Agriculture: Implications for Health, Environment and Regulation', 28–29. June 2018)

Regulators should probably review their escalating information requirements and consider the introduction of multi-tiered assessment approaches to make their own in-house processes sustainable for the increasing pace of technological innovations.

The OECD Conference on Genome Editing did not intend to deliver recommendations, because any initiation of policy development or harmonisation activities continues to fall to the relevant OECD Committees and governments. However, by way of a conclusion of the overall discussion in the room, regulatory approaches to genome editing should be determined to achieve policy objectives considering both precaution and innovation through better communication by all stakeholders. Furthermore, it is vital that different jurisdictions understand their respective regulatory and policy approaches to genome editing. This does not mean that there can be a uniform global approach, but that a common understanding is a prerequisite in minimising difficulties arising through different approaches.

Disclaimer Statement

The opinions expressed and arguments employed in this paper are the sole responsibility of the authors and do not necessarily reflect those of the OECD or of the governments of its member countries.

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Science & Society

Translating Biofabrication to the Market

Pedro F. Costa[1,*]

Biofabrication holds great potential to revolutionize important industries in the health, food, and textile sectors, but its translation to market is still challenging. I analyze

the current state of innovation and commercialization in biofabrication and try to assess its limitations, strengths, and future progress.

Biofabrication: Additive Manufacturing for Biology

Biofabrication can be generally described as the process of generating biological or biological-related structures, which may possess complex architectures/compositions and which are often generated by relying on highly automated tools such as 3D bioprinting and bioreactors [1–3]. 3D bioprinting is essentially similar to 3D printing, comprising the computer-assisted deposition of one or multiple materials (inks) in a layer-over-layer, highly organized manner. However, instead of employing materials conventionally used in 3D printing, it typically employs specialized bioinks, which are biocompatible or bioinert and which may contain special active biological components such as living cells and bioactive agents. Most conventional bioprinting technologies can directly deposit very sensitive and volatile bioink components such as cells and bioactive agents without damage [4], but other, harsher technologies follow indirect or multistep strategies where bioprinted constructs are complemented with cells and active agents at a later stage. Bioreactors are highly automated devices that allow the efficient culture, expansion, and differentiation of cells in particularly controlled *in vitro* environments in an accurate and repeatable manner [5]. Bioreactors can be acquired off the shelf or custom made according to specific requirements by resorting, namely, to additive manufacturing/3D bioprinting technologies [6]. Nonetheless, biofabrication still faces challenges, such as the need for GMP facilities, standardization/quality control measures, and changes in cell culture and reagent sources and culture cocktails.

Applications of Biofabrication

The applications of biofabrication technologies are nearly limitless. Given its high level of accuracy and repeatability enabled by automation, biofabrication is increasingly regarded as a central methodology for the future of tissue engineering and regenerative medicine (TERM) as well as in other fields such as drug discovery/development or even in the production of lab-grown meat and leather. The field of TERM is undoubtedly the one where biofabrication has had the greatest impact so far. Multiple types of human/animal tissue constructs have been recreated *in vitro* thanks to the contribution of biofabrication tools [7] and many more are expected in the future. Furthermore, it has become possible to implant such constructs in humans and animals and regenerate/reconstruct tissues that had been damaged or lost due to disease or trauma [8]. Some of the most important advantages of biofabricated constructs compared with conventional implants are the ability for them to be personalized according to the host's individual defects, to slowly biodegrade while being replaced by the host's tissues, and to include prevascular structures to overcome nutrient diffusion limitations found in large TERM constructs (Figure 1A). Biofabrication is also increasingly seen as the ideal solution for limitations encountered in the generation of *in vitro* models because it can accurately deposit and assemble specific materials (including cells) into complex 3D constructs that in turn can be accurately cultured, stimulated, and analyzed in bioreactors. Some remarkable examples of biofabricated complex tissue models have been developed for cardiovascular (Figure 1B) [9] and nephrological applications (Figure 1C) [10].

Other new, exciting applications for biofabrication are the artificial production of leather, by employing genetically modified collagen-producing yeast, and meat, by growing stem cell-differentiated muscle in bioreactors. Meat biofabrication may be as impactful as biofabrication in TERM since it may revolutionize an immense industry deeply intertwined with human nutrition. Despite foreseen high adoption costs and regulatory hurdles [11], if this new way of producing meat indeed becomes mainstream, it will not only be able to mimic existing meat but will also (and maybe more importantly) enable the production of inexpensive (US$5/kg) (https://www.fastcompany.com/40565582/lab-grown-meat-is-getting-cheap-enough-for-anyone-to-buy) and healthier food, with enhanced flavor, texture, and nutritional properties through a faster, more resource-efficient and less polluting process. Similarly, automated biofabrication processes will also enable the manufacture of leather equivalents by means of simpler, faster, and cleaner industrial processes reducing livestock production, which occupies 30% of global land surface and generates 15–24% of global greenhouse gas emission.

Innovation in Biofabrication

Despite biofabrication's hi-tech character, its underlying innovation process has so far been quite simple. Following the classification system established by Pisano (Figure 1D) [12], innovation in biofabrication can be generally classified as routine innovation since it brings forward neither a revolutionary new technology (not radical) nor a revolutionary new business model (not disruptive). It results instead from the merger of multiple existing technologies. Bioprinting technologies, for example, have evolved from existing 3D printing technologies through modifications of the materials employed and their deposition mechanisms. One exception is the production of leather and meat which, despite applying conventional biofabrication technologies, is directed at unconventional applications. In this case, the innovation process could instead be classified as radical, since the generation

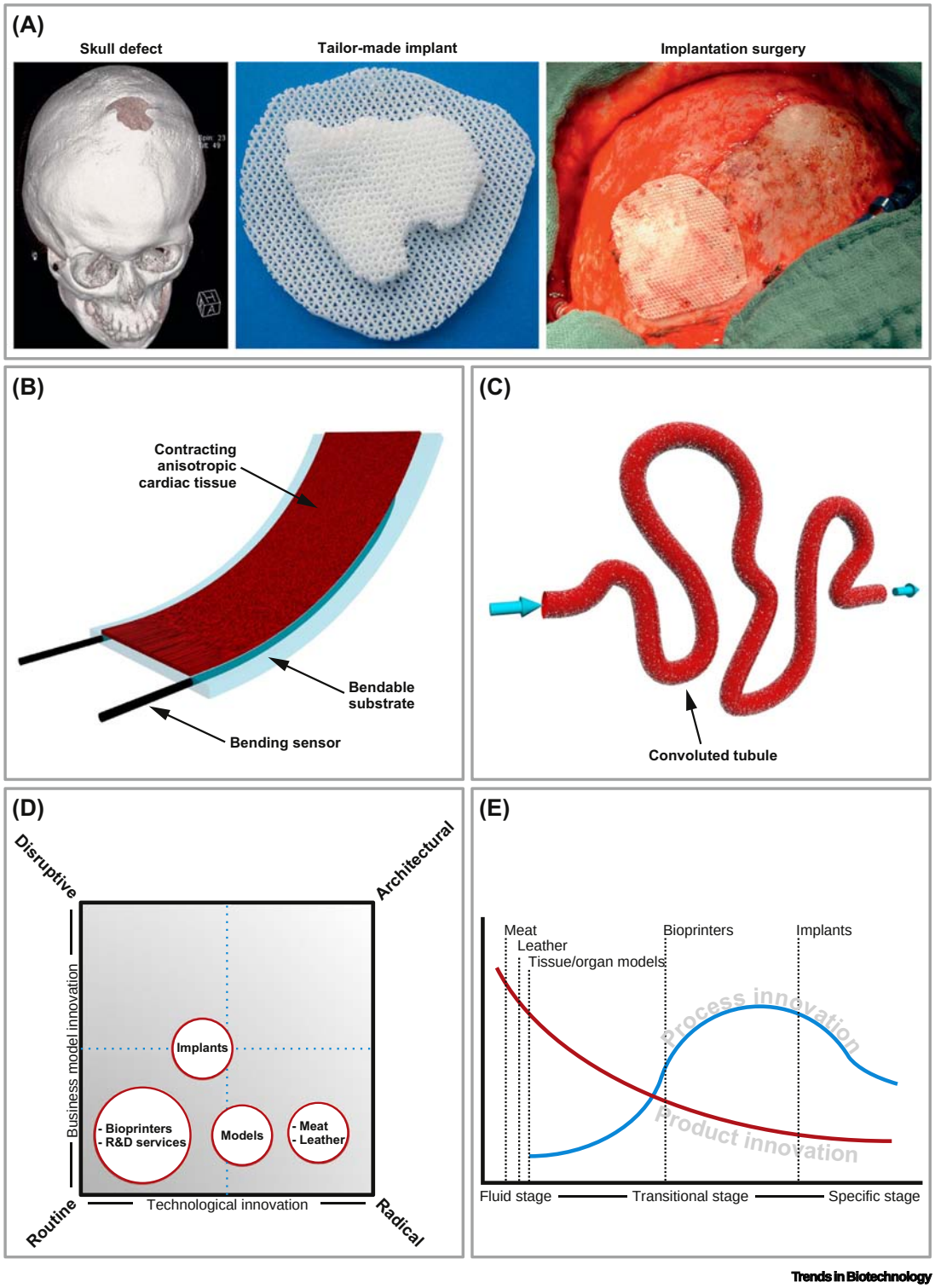

Figure 1. Applications and Innovation in Biofabrication. (A) Custom-made implant. Adapted, with permission, from [8]. (B) Beating cardiac model [9]. (C) Perfusable nephrological model [10]. (D) Types of biofabrication-based innovation according to the classification system established by Pisano [13]. (E) Stages of biofabrication-based innovation according to the classification system developed by Utterback and Abernathy. Adapted, with permission, from [14].

of the future products proposed involves a high level of novel technical competence, does not resemble anything else currently in the market, and could have a transformative impact on current production methods.

Biofabrication's business models are not particularly novel either, simply providing products and services in rather conventional ways. However, 3D bioprinted implant companies do add an innovative factor by enabling personalization/customization prior to implantation. This can be considered an early type of product–service system business model where, due to the highly specific nature of the problem, the customer is offered an integrated solution comprising both the final product (personalized implant) and the required personalization service to generate the product. All other business models employed by biofabrication-related companies mainly focus on either providing bioprinting equipment – like any other laboratory equipment – or providing R&D services.

According to the classification system developed by Utterback and Abernathy (Figure 1E) [13], biofabrication can be considered as still going through an early fluid and/or transitional stage of innovation. Customized biodegradable implants, which have developed over several decades in tandem with standardized metal implants toward personalization/customization, are the only products that may be considered to be close to standardization. Furthermore, regulatory constraints have forced these products to tightly fit into preexisting standards, expediting commercialization for medical purposes. Besides the bioprinter business, which is undergoing an early transitional stage due to the relative simplicity of its products, all other types of biofabrication businesses are going through a fluid stage. Such products and services are still highly variable and in constant change, in an early stage of development, often between the laboratory and the market.

Commercialization of Biofabrication

Biofabrication's state of commercialization results from its early stage of innovation. A growing number of companies (see Table I in Box 1) are entering this market by focusing on diverse applications and employing various business models (Box 1). The business of customized biodegradable implants has become relatively mature in a highly profitable niche market. However, biofabricated biodegradable implants are yet to prove their worth as an advantageous business case for hospitals, insurers, and health systems worldwide, compared with equally customizable metal implants currently provided by well-established international corporations, by emphasizing their unique ability to fully regenerate (not replace) tissues. The bioprinter business is likely to follow a path of narrowing product offer toward a small number of dominant designs. Increased standardization, manufacturing optimization, and competition among incumbents for market share will make bioprinters less expensive, therefore becoming commonly available laboratory equipment. Furthermore, the business model for bioprinters may eventually resemble the business model for 2D printers where, on standardization, the development and sales of ink cartridges became the industry's main source of revenue.

The business model for biofabricated meat for human consumption will still require some regulatory scrutiny, which is often uncertain and often delays the commercialization of novel biotech products. However, some precedents provide reasons for optimism, such as meat derived from cloned animals which, despite its novelty, has been approved by the FDA and the US Department of Agriculture. Being less regulated, biofabricated leather will be comparatively easier to introduce in the market, depending mainly on user and industry adoption and adequate pricing.

The business of tissue/organ models can be seen as a multistage process. Given that these models are currently meant primarily for research purposes, they are not required to go through a high level of certification and/or regulatory scrutiny. Eventually, however, this technology is expected to become an important tool in diagnostic and personalized medicine, as well as robust and reliable drug screening platforms (as alternatives to animal models), where regulatory scrutiny is extremely demanding. Many biofabrication-based tissue/organ models are currently under development by various entities (academic and non-academic), reflecting a strong research demand. Currently, tissue/organ model companies must provide flexible and adaptable solutions to meet a large variety of user-defined requirements in a still-undefined market. On the validation of a number of models, the market will adopt – and most likely combine – the most relevant ones to mimic the full complexity of the human body. At that point, it will also be necessary to implement 'smart' computing capabilities to automatically acquire, process, and interpret large quantities of data generated from within such models.

In conclusion, biofabrication as a whole is on the right track to commercialization but still in a quite early stage. In the next few years, its translation is expected to accelerate, resulting in an increasingly wider availability of biofabrication-based products in the market.

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REVIEWS

Box 1. Main Biofabrication-Based Companies

Biofabrication technologies are slowly being converted into businesses and promise to greatly advance manufacturing, economies, and health care [14]. As Table I shows, most biofabrication-based companies are mainly focused on providing bioprinters. A growing demand from research laboratories combined with the adoption of the well-established business model employed in selling general laboratory equipment makes this a relatively 'easy' business. This led to successful business ventures such as Cellink's initial public offer (IPO) just 10 months after being founded. In the past few years, there has also been a strategic shift from pure organ/tissue bioprinting approaches toward tissue models. A clear example of this shift was observed in the company Organovo, which initially hoped to provide fully functioning implantable bioprinted organs/tissues in the near future but meanwhile, and until that becomes a reality, redirected its focus mainly to the production of model constructs aimed at aiding in drug discovery/development. Not only is the generation of *in vitro* models technically easier than generating full tissues and organs (in terms of both the size and the complexity of generated constructs), but it also faces much less regulatory resistance since *in vitro* models are, at present, mainly meant for research purposes and not for implantation.

Table I. Biofabrication-Based Companies Currently in the Market

Company name	Country	Main product/activity	Technology readiness level (TRL)
Osteopore	Singapore	Bioprinted bioresorbable implants	TRL 9
Organovo	USA	Bioprinted tissue models	TRL 9
Cyfuse Biomedical	Japan	Cellular spheroid fusion platform	TRL 9
Modern Meadow	USA	Biofabricated leather	TRL 4
AlephFarms	Israel	Biofabricated meat	TRL 4
Future Meat Technologies	Israel	Biofabricated meat	TRL 4
Memphis Meat	USA	Biofabricated meat	TRL 4
Mosa Meat	Netherlands	Biofabricated meat	TRL 4
Nano3D	USA	Magnetic bioprinting technology	TRL 9
Allevi	USA	Bioprinter manufacturer	TRL 9
Cellink	Sweden	Bioprinter manufacturer	TRL 9
Aspect Biosystems	Canada	Bioprinter manufacturer	TRL 9
3D Bioprinting Solutions	Russia	Bioprinter manufacturer	TRL 9
Rokit	South Korea	Bioprinter manufacturer	TRL 9
Regemat	Spain	Bioprinter manufacturer	TRL 9
RegenHU	Switzerland	Bioprinter manufacturer	TRL 9
Envisiontec	Germany	Bioprinter manufacturer	TRL 9

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Spotlight

Synthesis of Recoded Bacterial Genomes toward Bespoke Biocatalysis

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Ongoing efforts in synthetic biology aim at constructing (micro)organisms with (pre)defined properties. A recent breakthrough is the chemical synthesis of a recoded *Escherichia coli* genome by Fredens *et al.* (*Nature*, 2019). Besides the conceptual and technological *tour de force*, the consequences of this unprecedented effort for whole-cell biocatalysis are multifold.

Continuous technological advances in DNA synthesis have realized some of the most ambitious objectives of synthetic biology: the creation of organisms carrying synthetic