Biointelligent Manufacturing

Definitions, International Status, Potentials for Europe and Recommendations

Whitepaper of the Manu*FUTURE* sub-platform
Biointelligent Manufacturing (BIM)

MANU*FUTURE*-EU

BIM
Biointelligent Manufacturing

Contents

1. Executive Summary

Production technology plays a decisive role in the European Union; it is the backbone of the European manufacturing industry, creating value and securing European competitiveness. Continuous innovation of production is therefore a key success factor for Europe. The European manufacturing industry is both a provider and a user of new technologies, a core enabler of progress and prosperity. It helps to ensure that the diversity of products that surround us in our everyday life make it to market while being affordable for all members of the society. Staying competitive globally requires constant development of new processes and technologies and adaptive organizations. Today it is the rapid development in life sciences that is giving the industry new impetus across the entire process and value chain, opening new innovation spaces in order to achieve the world's sustainability goals.

Digitalisation and Industry 4.0 technologies with nature-like distribution of control and enhanced communication between the control entities, are currently powerful drivers for industrial innovation and the necessary basis for the European Commission's priorities on human centricity and sustainability objectives.

With the challenges humanity faces currently, it is widely agreed that any industrial transformation must include regenerative features, an inherently social dimension, and an environmental dimension.

Nature is a role model in this respect, in terms of efficiency, effectiveness, circularity, and self-organisation. The vision of Biointelligent Manufacturing is to not only copy but integrate and interact with biological systems in man-made technical and information systems. On one hand, this implies implementing capabilities in technical systems that could not be mapped technically until now. And on the other hand, it makes the production of goods resource-efficient and ecologically sustainable.

In 2020, the European Technology Platform Manu*FUTURE* established the sub-platform Biointelligent Manufacturing (BIM), which calls on all relevant stakeholders to develop innovative research strategies to support the biological transformation of manufacturing, based on and taking further the digital transformation.

The novelty of the biological transformation is in bringing technical systems, information systems and biological systems into close trilateral interaction. This whitepaper shows the creation of novel solution spaces at the nexus of the three disciplines and proposes measures to exploit them in a structured way.

The arising ecosystem for Biointelligent Manufacturing needs to integrate multiple stakeholders and to ensure their participation. Translational centres that bridge the gap from pilot plant to industry scale, and interactive creation spaces will help foster technological progress and allow market access to new players in the field. Agile funding formats will further help accelerate this process and to ensure companies' access to new market segments. In addition to public funding, activation of an innovation-oriented capital market by mobilizing private and venture capital is essential.

The promotion of innovation and communication by interdisciplinary research projects involving science, the private sector, civil society, and politics, will be essential to this European innovation space. The education of specialists through interdisciplinary training and study offers as well as custom-fit training formats will form the educational backbone. Creating and coordinating all the recommended activites is a huge and complex task for all stakeholders. Performing well, this new paradigm of Biointelligent Manufacturing will provide many new "natural" paths to a competitive sustainable development of Europe.

2. Introduction

The European manufacturing industry helps to ensure that the diversity of products that surround us in our everyday life make it to market and are affordable – whether yoghurt or t-shirts, cars or energy solutions. The production chain ranges from raw and recycled materials, components, software and hardware to those products and associated services and maintenance up to remanufacturing and recycling, utilising tools, machinery, equipment, automation, and logistics. The manufacturing industry is both a provider and a user of new technologies, a core enabler of progress and prosperity.

To remain competitive, it is essential to constantly develop new processes, technologies and organisations. After digitalisation and Industry 4.0, today it is the rapid development in life sciences that is giving the industry new impetus across the entire process and value chain. The imitation and integration of biological systems in human made technical and information systems, but even more the interaction between them, is opening new innovation spaces and enables new opportunities to achieve the world's sustainability goals.

In 2020, the European Technology Platform Manu*FUTURE* established the sub-platform Biointelligent Manufacturing (BIM), which calls on all relevant stakeholders to develop innovative research strategies in supporting the transformation of industrial manufacturing by biological entities and principles – the convergence of biology, technology, and information technology in manufacturing and manufactured goods. This convergence holds great promise for highly disruptive innovation for emerging technology and sustainable development. Today, about 100 stakeholders from 16 countriesare working togehter in this subplatform to develop appropriate innovative research strategies. This white paper summarizes the results of the discussions in the three working groups on "Research and Technology Development", "Industrial Applications and Business Models", and "Skills and Education".

The objectives of this white paper are:

- To show the potential that biology can bring as a new dimension to the manufacturing sector, to industry and society – a biological transformation as the next wave after – and based on – the digital transformation
- To set the scene for both the motivation and drivers of the biological transformation, as well as Europe's considerable advantages in this context
- To reveal "biointelligence" as a new merger of technical, IT and biological systems: differentiating the existing fields of biotechnology, bioeconomy and bionics
- To elaborate a viable, agreed definition for Biointelligent Manufacturing and identify its building blocks through powerful examples of products and production, as well as best practices
- To define fields of innovation based on biointelligence for the manufacturing sector in Europe, building on and complementing the Manu*FUTURE* Vision 2030.

MANU*FUTURE*-EU

- Manu*FUTURE* is a European Technology Platform (ETP) established in 2003 as "an industry-led stakeholder forum recognised by the European Commission as a key actor in driving innovation, knowledge transfer and European competitiveness".
- "The mission of Manu*FUTURE* is to propose, develop, and implement a strategy based on research and innovation, which is capable of speeding up the rate of industrial transformation to high-added-value products, processes, and services in order to secure high-skills employment and win a major share of the global manufacturing output in the knowledge-driven economy."

3. Vision

The vision of the Manu*FUTURE* sub-platform Biointelligent Manufacturing is to lead European companies and research institutions into the new era of Biointelligent Manufacturing that aims towards sustainability, digitalisation, and technological progress, drawing from the understanding of biological systems to strengthen the EU as the leading region of future production.

Nature is a role model in this respect, in terms of efficiency, effectiveness, circularity, and self-organisation: What nature has produced in 3.5 billion years of evolution is still technically unimaginable for us. Biological systems can build themselves, reproduce, organise themselves, react extremely quickly to external influences, and are extremely efficient in terms of energy. Even the simplest organisms have molecular motors with an efficiency of almost 100 %. Bees and moths can localise odours over long distances by means of extremely sensitive olfactory sensilla via odour and time gradients. In nature, we find hair cells even in the smallest creatures, where a change in the synaptic signal can be measured even at a deflection of one Ångström. Incredibly complex structures with a myriad of complex synthesis processes are completely self-organised in every living being, based on genetic DNA „blueprints“ and a huge number of regulatory processes.

The vision of Biointelligent Manufacturing is to combine these biological systems with man-made technical and information systems. On one hand, this implies implementing capabilities in technical systems that could not be mapped technically until now. And on the other hand, it makes the production of goods resource-efficient and ecologically sustainable. Importantly, the introduction of biology as a new dimension for the transformation of industrial processes in addition to engineering and ICT offers a great opportunity to solve the challenges humankind faces. Natural principles and components will enlarge the solution space and lead to new transformative capacities in terms of circularity and sustainability.

Europe has a unique selling point for translating this vision into new production ecosystems that support the goal of achieving sustainable manufacturing. Profound progress in the area of life sciences and related areas has reached European research institutions and companies. At the same time, Europe is traditionally strong in production research, development and applications. Three million employees in 80,000 companies make up the European machinery industry, achieving revenue of 730 billion Euro, out of a total of 2,710 billion Euro worldwide. The combination of the diversity of our regions, cultures, and approaches; the dense network of researchers, start-ups and mature companies of all sizes; as well as a wide-ranging presence in worldwide markets and the enormous internal market for all kinds of products makes Europe different and highly competitive with other regions of the world. These points form the cornerstone of a deeply rooted domain expertise in Europe and a vibrant production ecosystem. Finally, Europeans share common values: Pluralism, tolerance, justice, solidarity, non-discrimination, and equality, all of which translates into a commitment to responsible research, corporate social responsibility, protection of environment and nature, as well as sustainable finance.

The vision of sustainable Biointelligent Manufacturing is that it both enables and requires the development of new production ecosystems. These will be achieved by a transformation of established industries throughout Europe, providing a fertile environment and guidelines for companies, SMEs, and start-ups, fostering Europe-wide, multi-disciplinary dialogue and knowledge transfer.

4. Biointelligent Manufacturing – Delineation and Definition

4.1. Structuring the Bio World for Manufacturing

When talking about “Bio”, which involves plenty of new termini, public communication can be quite confusing: from Bionics to Bioeconomy, from gene sequencing and synthetic biology to organic food, from biologicalisation to bioinspiration. This heterogeneity of terms recalls the similar situation with “digitalisation” for manufacturing in the 2000s, before the terms Industry 4.0 and Smart Manufacturing were established. This whitepaper proposes a structured differentiation of terms and a definition for the key term Biointelligent Manufacturing.

Several approaches can be taken to structure the “bio world” and terms that come with it. First of all (clause 4.2), we show the big picture on demand, supply, and international players: motivation and drivers for a biological transformation. Second (clause 4.3), the holistic picture of the change of industrial value creation through a biological transformation is drawn from bioinspiration to biointegration to biointelligence. This not only takes the industry into account, but also extends to society. The third approach (clause 4.4) takes the view of the process chain, a very intuitive view for industrial engineering: to transform material through a machine with a control into a product. Any step within this process chain can be “bio” or “non-bio”. In this way, an uncomplicated classification can be made and an entire set of new manufacturing paradigms are revealed. These two latter parts form the “definitions” section of this paper. We will show examples for products and production, from 3D-printed living tissue to microorganisms that recycle rare earth metals, from deep learning through artificial neural networks to data storage made from DNA.

4.2. The Big Picture: Motivation and Drivers

What are the motivations and drivers for the biological transformation? If we take a step back and look at the challenges humankind is facing today, it is wise to take a look at the tools we have and the key players we need to master those challenges internationally. If we consider the challenges on the demand side and the available tools in worldwide communities on the supply side, we can take an objective, problem-solving approach. If we put the needs for European competitiveness on the top, technological sovereignty and European values come into play.

Demand Side: Solving Challenges for Humankind

As early as 1972, the Club of Rome published “The Limits to Growth”. Today, humankind is faced with the urgent and critical question of how to achieve prosperity for all without overburdening the planet‘s natural resources. The question of how to satisfy the needs of future generations with regard to nutrition, health, habitation, energy, or resources is of tremendous concern, especially in terms of population growth and global consumption. This is a challenge for industry and society alike, and affects the manufacturing sector as an enabler in particular.

Sustainability is a powerful driver here. The UN Sustainable Development Goals and the EU Green Deal have brought it further into focus, and sustainable finance is increasingly becoming a benchmark for the allocation of capital. In order to meet these requirements, moving towards a circular economy, sustainability, and corporate social responsibility is essential. There is no doubt: the demand for new solutions is high. Digitalisation and other Industry 4.0 technologies are inevitable requisites. But there are still many more options to explore. Different approaches will be taken by different players. Nevertheless, all approaches and players are united in solving the problems we face currently and over the decades to come.

Supply Side:
New Enabling Technologies

Biology as a new dimension in technical systems opens up a completely new innovation space for sustainable industrial value creation. Nature as a role model is at the core of circular economy and bionics. Nature as a supplier of raw materials is the basis for bioeconomy. Beyond that, new opportunities are rapidly emerging: an ever better understanding of biological processes has created new powerful biological and biochemical tools.

New methods for synthetic biology and genetic engineering of organisms have become available at affordable prices. The cost of decoding the human genome has dropped from 100 Mio. US$ in 2000 to below 1,000 US$ today.[1] Advanced computational resources enable better analysis and understanding of biological processes. CRISPR/Cas "gene scissors" have enabled modification of organisms' genomes, i.e., a cell's DNA or RNA. Programming and reprogramming of the genetic code have become possible and have enabled impressive new applications like long-term data storage with DNA.[2] Using new biology/technology interfaces provides new sensors such as the artificial nose, using living neurons sniffing for drugs.[3] Recent advances in micro- and nanoscale manufacturing allow for new product classes. Life sciences, more than any other business field, have achieved significant growth, thanks to the advances in engineering, electronics, and IT, and due to increasing needs of an ageing society. We must keep in mind that ethical questions and acceptance in society must also be addressed.

Due to the rapid growth of the life science knowledge and market, there is plenty of bio-competence already. The combination of bio-competence, related disciplines and the targeted use of this knowledge to achieve biological transformation in manufacturing is a major challenge yet to be realised. To speed up this development, we must seriously examine the current status and future prospective of the field.

International Efforts: A Worldwide Race

Competition promotes innovation. And innovation challenges competition. Therefore, an excellent goal is to strive for the best solutions at every step that are affordable and most resource-efficient, with the overarching objective of sustainability. Economy and ecology must go hand in hand. Competitiveness is critical for all market players. Open markets are the key to a successful economy, especially for the manufacturing sector. One essential condition across the spectrum: a global, level playing field.

The number of innovations and patents in biotechnology is rapidly increasing. Now it is time to harvest the fruits to master the challenges described above – thereby increasing the competitiveness of industry. Whether in research and development, industrial applications and business models, or skills and education, governments and companies face a worldwide race to stay ahead of the pack. Current problems in the worldwide supply chain – and tendency towards protectionism – have increased the impetus for technological sovereignty to maintain jobs and ensure prosperity, also in the EU. On the other hand, open innovation can be the key to significant technology breakthroughs. Research and innovation can develop greatly, but only within international partnerships and through exchange of knowledge. The international space station or the human genome project are guiding stars in this respect. It is evident that there must be a balance of technological sovereignty and international collaboration, also for Biointelligent Manufacturing.

1 https://www.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost

2 https://dnastoragealliance.org

3 https://koniku.com/

Important players that provide new solutions taking advantage of biology can be found in Europe, America, and Asia, especially in the EU, US, Canada, Israel, China and Japan. In addition to big corporations that apply biology, SMEs – and especially start-ups – often have the chance to try out new technologies more creatively and with an unbiased mindset, and can bring new products to the market faster. This is also the case for bio-related products and production technology. Private and public financing is available, but not equally distributed. Access to finance is essential for any innovation, especially in risk-averse regions, and with regulation in effect for research and products, e.g., pharmaceuticals. Biointelligent Manufacturing also offers ample opportunity for developing countries. In contrast to full automation, biointelligent solutions can be better adapted and tailored to particular, local needs.

There is an additional driver for accelerating Biointelligent Manufacturing: the international race has been on for a long time. Now it is the time to ensure that the EU stays ahead.

The Way to Go: An Additional Dimension for Industry 4.0

Digitalisation and Industry 4.0 have been great drivers for the manufacturing industry in the last two decades, merging mechanical and electrical engineering with information and communication technologies (ICT). Self-organizing production was a catch word in the early days, and increasing efficiency and decreasing costs has been the major objective. But with the challenges outlined above, optimising the total cost of ownership alone is not any longer the primary goal. Engineering and ICT are reaching their limits, even with artificial intelligence (AI) as the current push. Economies of scale must be complemented by circularity and sustainability. Rebound effects such as increasing energy needs for digitalisation must be avoided. In fact, nature was initially part of the description of Industry 4.0, but, as recently stated, the narrative shifted away “turning nature into the forgotten half of the fourth industrial revolution”.[4] Furthermore, the development of digitalisation and automation to assist the human workforce have been a central topic from the very beginning. The European Commission has recently labelled digitalisation of industry with human centricity and sustainability objectives as Industry 5.0, to explicitly outline these priorities, which have been more implicit in Industry 4.0, and which are important to achieve Europe’s 2030 goals. Industrial transformation must include regenerative features, an inherently social dimension, and an environmental dimension.[5]

The way forward is clear: sustainable industrial value creation is the basis for the next leap forward of the manufacturing industry. In the future, there will be an ever greater demand for a technology-based economy that is geared to current needs of people and planet.

4 Nature Co-Design: A Revolution in the Making., BCG Reports 2022, https://www.bcg.com/publications/2021/why-nature-co-design-will-be-so-important-for-the-next-industrial-revolution

5 European Commission, Directorate-General for Research and Innovation, Renda, A., Schwaag Serger, S., Tataj, D., et al., Industry 5.0, a transformative vision for Europe: governing systemic transformations towards a sustainable industry, Publications Office of the European Union, 2022, https://data.europa.eu/doi/10.2777/17322

4.3. The Holistic View: The Biological Transformation

Biological transformation refers to the shift towards a new technical basis for a sustainable economic system, one of the key enablers for both a healthy society and a competitive industry. If bioeconomy is interpreted as the state of a future sustainable economic system (which requires consideration of all sectors of the national economy), then the biological transformation describes the process of creating its technical basis. As such, the term „biological transformation“ describes a process that is manifest in a multitude of activities. It goes without saying that many of these activities are not „novelties“, but will only achieve their full potential and a social change through the systematic and integrated application of existing concepts, technologies and procedures. In order to place the topic at the European level, it's simply not sufficient to re-name ongoing activities.

Engineering and automation have been part of biotechnology for quite a while. Additionally, digital tools and digital twins have already been applied. Likewise, there were digital tools in engineering.

The novelty of biological transformation is in bringing technical systems, information systems and biological systems into close interaction, whereas they previously only cooperated bilaterally (Figure 4.1). This leads to the creation of novel solution spaces at the nexus of the three disciplines. Similarly, the term technology convergence has been discussed previously.

Technological convergence generally refers to the trend or phenomenon where two or more independent technologies integrate and form a new outcome.[6 7]
The first publications addressing biological transformation of industry and manufacturing appeared in 2018.[8]

The "Biologicalisation of Industry" was described by Byrne et al., who defined this field as "the use and integration of biological and bio-inspired principles, materials, functions, structures, and resources for intelligent and sustainable manufacturing technologies and systems with the aim of achieving their full potential."[9] Miehe et al. define the term biological transformation of industrial value creation according to Patermann as "a systematic application of the knowledge of nature and/or natural processes aiming at optimizing a manufacturing system regarding its societal and business challenges by seeking a convergence of bio- and technosphere".[10]

Consequently, there is need for new concepts and technologies that can actively contribute to biological transformation in the field of advanced manufacturing. Biointelligent Manufacturing systems, on the other hand, do not describe a process, but are physical entities that are still to be developed. It's instruments are bioinspiration (primarily bionics/biomimetics), biointegration (primarily biotechnology and process engineering) and biointelligence (promoting bioinspiration and biointegration approaches with the help of molecular and digital technologies).

6 https://www.taylorfrancis.com/books/mono/10.4324/9781315574127/convergenomics-sang-lee-david-olson

7 https://jopeninnovation.springeropen.com/articles/10.1186/s40852-017-0074-z

8 https://www.sciencedirect.com/science/article/pii/S2212827118306012

9 Gerald Byrne, Dimitri Dimitrov, Laszlo Monostori, Roberto Teti, Fred van Houten, Rafi Wertheim, Biologicalisation: Biological transformation in manufacturing, CIRP Journal of Manufacturing Science and Technology, 2018, 21,1-32, https://doi.org/10.1016/j.cirpj.2018.03.003.

10 Robert Miehe, Thomas Bauernhansl, Oliver Schwarz, Andrea Traube, Anselm Lorenzoni, Lara Waltersmann, Johannes Full, Jessica Horbelt, Alexander Sauer,The biological transformation of the manufacturing industry – envisioning biointelligent value adding, Procedia CIRP, Volume 72, 2018, Pages 739-743, ISSN 2212-8271, https://doi.org/10.1016/j.procir.2018.04.085.

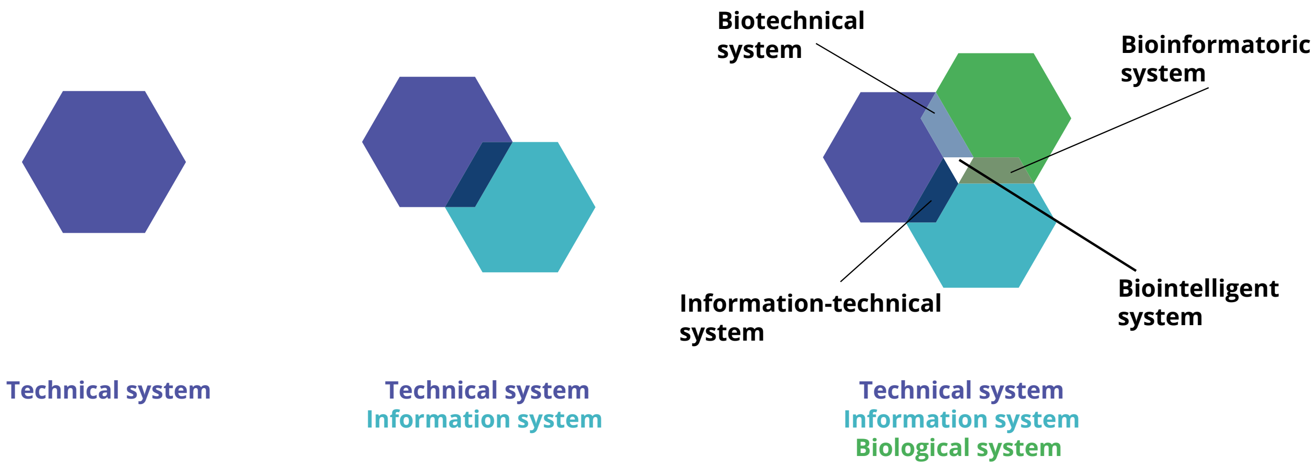


Figure 4.1 *Trilateral technology convergence to biointelligent systems*

Bioinspiration

Mankind has always taken advantage of natural resources and taken inspiration from nature. A circular economy uses nature as a role model. Bioinspiration for technical products is called bionics and was widely introduced, e.g., by Leonardo da Vinci's flight apparatus and by Wilhelm Barthlotte's Lotus effect for glass or shark skin for airplanes.

Bioinspired research is a return to the classical origins of science: it is a field based on observing the remarkable functions that characterise living organisms, and trying to abstract and imitate those functions in technical systems.

The observation of nature has led to the early developments of bioinspired products such as novel materials, devices, and structures inspired by solutions in biological systems. Biological evolution and refinement has occurred over millions of years.[11] The main goal of the bioinspiration approach is to improve modelling and simulation of the biological system to attain a better understanding of nature's critical structural features for use in future bioinspired designs and functionalities.[12]

A more recent approach is an effort to recreate the complexity of the natural world in the digital world. It started with the basic idea of Industry 4.0 to distribute intelligence and enhance communication between entities. It was taken further by neural networks, able to reconstruct the adaptive mechanisms of the brain. And today, scientists try to extend this technology beyond bio-inspiration and bio-integration, attempting to make systems intelligent and unlock the mystery of the exceptional stability of biological mechanisms.

Today, one of the most interesting concepts is obtaining sustainability and circularity from nature. The evolution

11 Sanchez, Clément; Arribart, Hervé; Guille, Marie Madeleine Giraud (2005). "Biomimetism and bioinspiration as tools for the design of innovative materials and systems". Nature Materials. 4 (4): 277–288, doi:10.1038/nmat1339. PMID 15875305;

12 Whitesides, G. M. , "Bioinspiration: something for everyone", 2015 Interface Focus. 5 (4) 150031, doi:10.1098/rsfs.2015.0031

of industry towards a sustainable economy uses the natural world as a model that has helped us direct our efforts intuitively towards evolving products and processes similar to the biological environment. This is driven by the hope that this technological evolution will transfer the same ability of the natural world to recycle and regenerate itself into new and more evolved forms to the technical world. The manufacturing industry is constantly evolving, trying to fully engage the "green deal" of the circular economy. It soon became clear that nature offers a very important field of inspiration for starting a process of radical change towards a sustainable economy, based on reduced waste and intensified repair, reuse, refurbishment and finally recycling for a continuous and increasingly responsible reuse. Nature is based on the principle of cyclical reuse, allowing it to evolve in the most differentiated forms and ways for the sole purpose of preserving itself. Based on this paradigm, industry of the future must be created from the key concept that what is produced must largely serve to create new products in a cycle that must be repeated as often as possible. The technologies required to achieve this goal will be increasingly advanced and complex and will require, as in nature, the coexistence and collaboration of ever more disciplines in order to decipher and solve the technical and scientific questions and challenges that will arise during this journey.

Biointegration

One approach humankind has used to interact with nature is biontegration. An example of this is the fusion of artificial and biological materials such as artificial bonding of living tissue to the surface of a biomaterial or dental implant, independent of any mechanical interlocking mechanism. Biointegration is an intermediate step between bioinspiration and biointelligence.

Biointelligence

The concept of biointelligence goes far beyond bioinspiration and biointegration. Biointelligent systems, products or procedures require not only a simulation or integration of biological components and principles but an intimate interaction of technical, information, and biological systems (Figure 4.1). Biointelligence not only includes innovative materials and biological systems but aims for technologies and principles that allow a direct communication and interface between technical and biological systems above all. This emerging paradigm in the evolution of digitalisation and the 4th industrial revolution (Industry 4.0) implies, a close interdisciplinary interaction between skills that, until recently, had almost no points of contact. The main actors in this new industrial transformation are life sciences (medicine/biology/etc.), engineering (automation/nanotech/etc.) and digital technology (big data/artificial intelligence/etc.). Each of these areas will bring in their competences, but the investment should be under one overarching interdisciplinary cooperative roof.

In order to be able to physically produce [biointelligent] products in a biointelligent manner, concepts and components for Biointelligent Manufacturing are needed.

4.4. Introducing the Biological Transformation to the Process Chain: Biointelligent Manufacturing

Various definitions for biointelligence – and thus Biointelligent Manufacturing – are in play within international research and political communities. Yet they all share the same vision: that biointelligence is generated by the convergence of biology, engineering, and information technology. However, as soon as descriptions for certain products or production processes are developed, multiple interpretations for these terms can arise. For example, the term "intelligence" itself allows for various interpretations and is not yet sharply defined. For the same reason, Artificial Intelligence (AI) is still not fully defined, although the community has found a distinction between "strong" and "weak" AI. We have a similar case here, although the scope and history of terms seem even wider. Example: Is beer brewing or an intelligent airplane winglet already biointelligent? Maybe not. Does it become biointelligent by adding AI in the production process? How much "intelligence" is needed to call a product or production biointelligent?

Biointelligence is a paradigm, namely the rigorous linking of information-driven intelligence, machines and factories with the development and establishment of new biological, medical, or therapeutic processes, and systems. Indeed, the term does imply "decision making".

Related Definitions

Biotechnology

Biotechnology is the integration of both natural sciences and engineering sciences to achieve the application of organisms, cells, or parts thereof, and molecular analogues for products and services.[13] Biotechnology has applications in many industrial areas, including health care (medical), crop sciences/agriculture or food, and non-food industrial processes (e.g. chemicals, materials).

Bioeconomy

The bioeconomy means using renewable biological resources from land and sea, such as crops, forests, fish, animals and micro-organisms to produce food, materials and energy.[14] It encompasses the transformation of an economy dependent on fossil raw materials to one based on renewable raw materials.

Bionics

Bionics describes the transfer of phenomena and principles of nature to technology. Bionics is thus distinct from bioengineering (or biotechnology), which is the use of living things to perform certain industrial tasks.[15]

Biomanufacturing/Bioproduction

Biomanufacturing/Bioproduction is the production of clinically and commercially important biological products and chemicals from living cells, such as biologics-based drugs, vaccines, or biofuels and biopolymers. Produced entities can be highly complex that they can only be manufactured in living systems or indeed are a living system.

Bioengineering

Bioengineering is a discipline that applies engineering principles of design and analysis to biological systems, biomedical technologies and bioproduction.[16]

13 IUPAC. Compendium of Chemical Terminology, 2nd ed. (the "Gold Book"). Compiled by A. D. McNaught and A. Wilkinson. Blackwell Scientific Publications, Oxford (1997). Online version (2019-) created by S. J. Chalk. ISBN 0-9678550-9-8. https://doi.org/10.1351/goldbook.

14 https://ec.europa.eu/info/research-and-innovation/research-area/environment/bioeconomy_en

15 https://www.britannica.com/technology/bionics

16 https://bioeng.berkeley.edu/about-us/what-is-bioengineering

A helpful way to organise the terminology is the symmetry that appears, when we take the definitions of Digitisation, Digitalisation and Digital Transformation and transfer it to their "bio"-equivalents, as shown in the following table:[17 18 19]

Proposal of a Symmetric Classification

Digitisation *"Replacement of numerical values from continuous to discrete"*	*Biologisation* *"Replacement from non-bio to bio (e.g. of a material)"*
Digitalisation *"Transition of companies, individual sectors, the industry to digital companies, individual sectors, industry"*	*Biologicalisation* *"Transition of companies, individual sectors, the industry to biointelligent companies, individual sectors, industry"*
Digital Transformation *"Transition of the entire economy and society to a digital economy and society"*	*Biological Transformation* *"Transition of the entire economy and society to a biointelligent economy and society"*

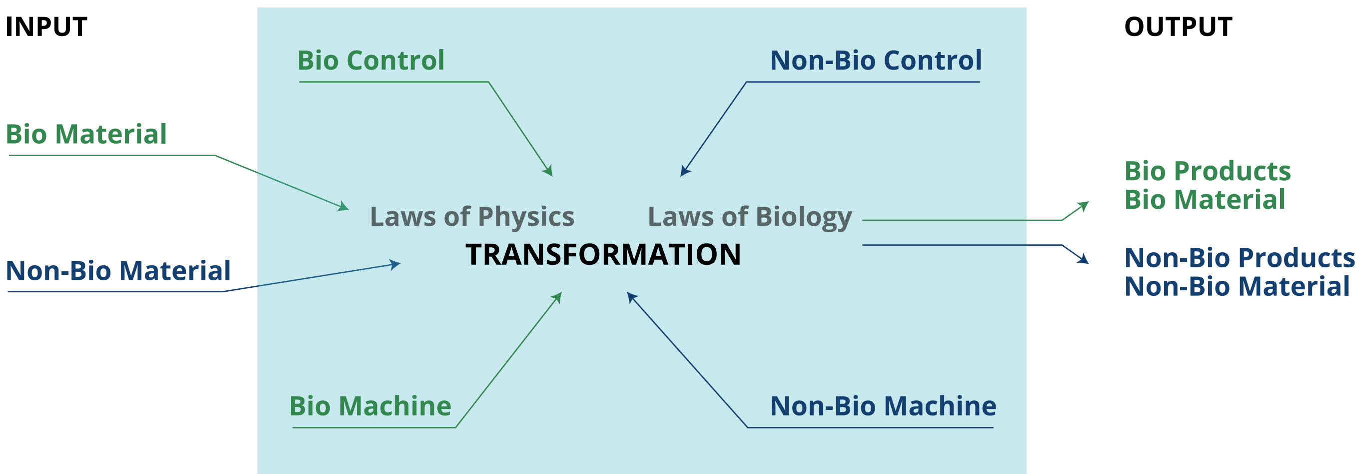


Figure 4.2 *Classification of steps in the process chain. (T. Tolio G. Trotta, 3rd ManuFUTURE Biointelligent Manufacturing plenary meeting)*

17 E. Maiser, VDMA Future Business Summit 03.09.2021, Stuttgart

18 https://www.forbes.com/sites/jasonbloomberg/2018/04/29/digitization-digitalization-and-digital-transformation-confuse-them-at-your-peril/

19 G. Byrne et al. "Biologicalisation: Biological transformation in manufacturing", CIRP Journal of Manufacturing Science and Technology, Volume 21, May 2018, Pages 1-32 | https://doi.org/10.1016/j.cirpj.2018.03.003

The figure above shows one very intuitive way of structuring products and production, allowing a simple means to introduce the "bio" component into the process chain. Every product is made in the following way, and it can be either bio or non-bio:

Transform a bio/non-bio material

through a bio/non-bio machine

with a bio/non-bio control

into a bio/non-bio product.

In this way, a straightforward classification can be made, from beer brewing (where microorganisms are "the bio-machine") and soft robots to DNA data storage. Circular economy and life cycle approaches can be portrayed just by adding several "transformation" boxes throughout a product life cycle. A whole set of new manufacturing paradigms is revealed (see below). With this view, a definition of biointelligence can be reached by defining how many process steps are required to be "bio" or "intelligent".

The comprehensive interaction of technical, informational and biological systems leads to the creation of completely new, self-sufficient production technologies and structures, so-called Biointelligent Manufacturing systems. A value-added system is considered to be biointelligent if there is at least one biological component in the product or production process. Also, an exchange of information between biological and technical components is now possible, even in real-time, via online self-learning process control and the existence of a digital twin. In comparison to the bio- and circular economies, which instead represent variations of sustainable subsistence strategies, biological transformation depicts a process of change that applies to the entire manufacturing industry.

Starting from the general definition by Byrne and from the approach proposed by Miehe et al., the biological transformation of value-additive systems may occur in different traits from bioinspiration to bio-interaction. The most advanced stage of Biointelligent Manufacturing – in which bio- and technospheres interact (see clause 4.3) – is seen as the area with the highest transformative capacity. But again, a common understanding across all manufacturing processes and across different industry sectors is still lacking. To enable a common understanding and know-how transfer of Biointelligent Manufacturing, we propose a classification of processes along two axes, as depicted in Figure 4.3. The horizontal axis differentiates between Physical and Control/Regulation (the "intelligence"), and the vertical axis differentiates between Artificial/Non-Biological and Biological. Compared to Figure 4.1, this classification consequently distinguishes not only in the physical aspect between technical and biological but also in the control/information/decision aspect. This differentiation considers the rapid development of controlling/utilising biological information systems in recent years. The four resulting quadrants classify the context areas:

- **Biological Process**, defined by the Biological and Physical directions, to identify the physical biological processes
- **Biological Control**, defined by Biological and Information/Intelligence, to represent the mind/control of the living organisms and therefore of biological processes able to generate control or even ideas and concepts leading to decisions;
- **Artificial Control**, defined by Information/Intelligence and Artificial, to represent how the artificial/technical world works through control, models, concepts, leading to decisions;
- **Artificial Process**, defined by Artificial and Physical, to represent artificial processes that interact in the physical world and with the physical laws that govern it.

While bioinspiration or integration can be realised with functions from only two quadrants, Biointelligent Manufacturing, as defined in this document and proposed as a general definition, utilises and puts into interaction at least three out of these four context areas. Examples of how concrete products and production processes can be classified using this definition are given in chapter 7.

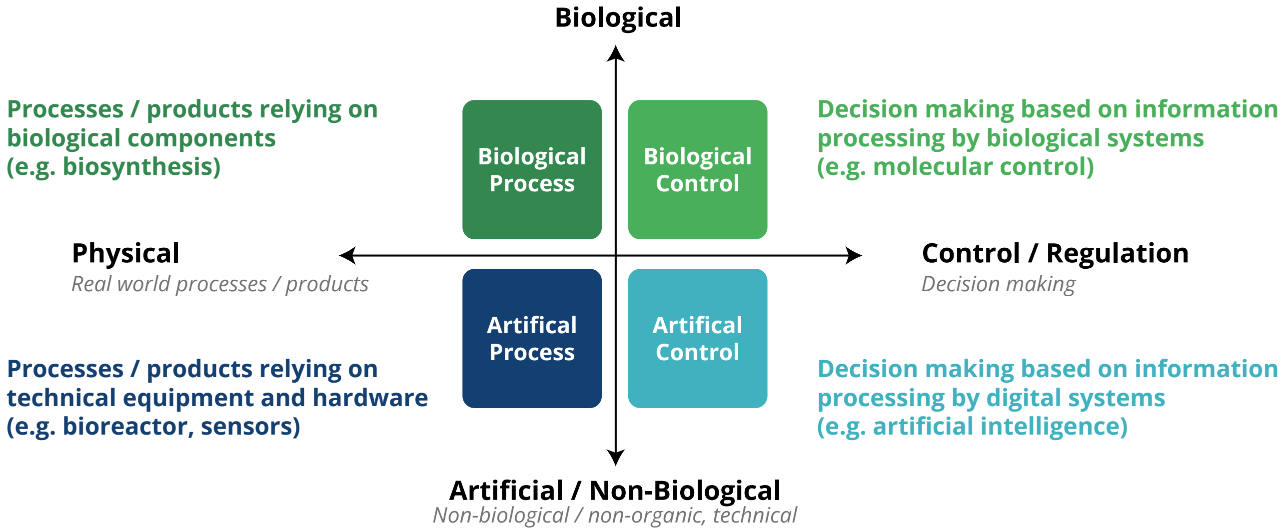


Figure 4.3 *Topology of Biointelligent Manufacturing, divided into four context areas*

5. A New Innovation Space of European Importance

With the above definition of Biointelligent Manufacturing and over-arching vision in mind, it is evident that linking biology, production technology and IT leads to a completely new innovation space of European importance. Inter- and transdisciplinarity will gain further importance and must be realised by collaboration across disciplines and national borders. Knowledge transfer across market segments will be as important as technology transfer and adaptation to new applications. Manu*FUTURE* will help to develop this innovation space by establishing a dialogue platform for DGs, national and regional ministries, industry, and research organisations.

The arising ecosystem for Biointelligent Manufacturing needs to integrate multiple stakeholders and to ensure their participation. Translational centres that bridge the gap from pilot plant to industry scale, and interactive creation spaces will help foster technological progress and allow market access to new players in the field. Agile funding formats will further help accelerate this process and to ensure companies' access to new market segments. In addition to public funding, activation of an innovation-oriented capital market by mobilizing private and venture capital is essential.

Last but not least, the promotion of innovation and communication by interdisciplinary research projects involving science, the private sector, civil society, and politics, will be essential to this European innovation space. The education of specialists through interdisciplinary training and study offers as well as custom-fit training formats will form the educational backbone.

Delivering on each of these measures will ensure Europe's technological sovereignty and positions Biointelligent Manufacturing as a much broader movement, which incorporates industrial production of any product type across every industry.

The creation of this new manufacturing ecosystem will ultimately help transform traditional industries throughout Europe; provide a fertile environment for growth; develop guidelines for companies, SMEs and start-ups; foster European multidisciplinary dialogue and knowledge transfer; and ultimately achieve a truly sustainable way of manufacturing – beyond simply swapping CO_2 certificates. Biointelligent Manufacturing contributes to an industrial transformation that aims for human-centred, sustainable industry at scale, with value chains that deliver societal and planetary wellbeing. A crucial element in achieving this vision is providing a new technological innovation space that opens the door to disruptive changes in manufacturing.

Other World-Wide Initiatives

The elaboration of the potential of biological entities for industrial value creation is not only of interest for Europe. Other world regions have developed their own activities to dive into the matter, with different focuses and approaches. Furthermore, regional initiatives have been formed, such as the "Biointelligence Competence Center", which pays on larger national efforts.

https://biointelligence-center.org/en

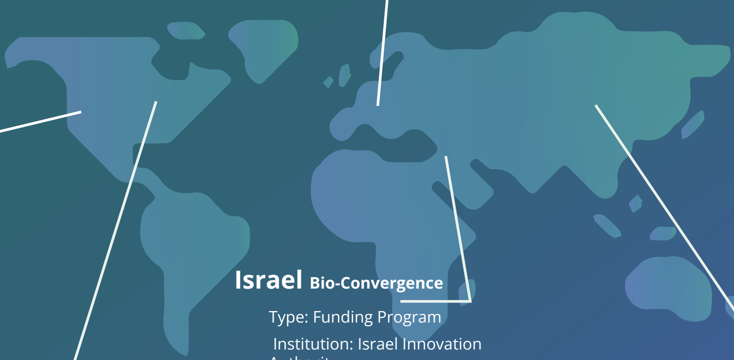
Europe Manu*FUTURE* sub-platform on Biointelligent Manufacturing

Type: Interest Group

Field: all application fields

Mission: Manu*FUTURE* has established a sub-platform on Biointelligent Manufacturing to involve all relevant stakeholders and develop innovative research strategies to foster the biological transformation of manufacturing.

Start: 2020



USA BioMADE, ARMI's BioFabUSA

Type: I: Manufacturing Innovation Institute

Institutions: Department of Defense, Manufacturing USA, Advanced Regenerative Manufacturing Institute (ARMI)

Field: Bioprocess industry

Mission: Building a sustain-nable, domestic end-to-end bioindustrial manufacturing ecosystem; make practical the large-scale manufacturing of engineered tissues and tissue-related technologies

Start: 2021, 2018

Israel Bio-Convergence

Type: Funding Program

Institution: Israel Innovation Authority

Field: Medicine, Life Science

Mission: Global health and medicine revolution is fostering a new multidisciplinary industry (biology & engineering)

Start: 2020

Canada Biodigital Convergence

Type: initial definition report and standardization activities

Institution: Policy Horizons Canada (strategic foresight organization in Government)

Field: All application fields

Mission: Foresight studies and standardization. IEC Standardization Evaluation Group (SEG) 12 on Biodigital convergence.

Start: 2019

China Chongqing Research Institute of Biointelligent Manufacturing

Type: Public research institute

Institution: Liangjiang New Area (authorities)

Field: Medicine, Life Science

Mission: Protect life and health, focus on biomedical materials, biomedical intelligent equipment, clinical implantable products, bioprinting technology

Start: 2021

References: biomade.org armiusa.org innovationisrael.org.il/en/reportchapter/bio-convergence publications.gc.ca/site/eng/9.881083/publication.html www.cibim.ac.cn www.biointelligentmanufacturing.org

5.1. Impact of Biointelligent Manufacturing for Individual Stakeholder Groups

5.1.1. Society

We are currently experiencing a triple crisis, caused by climate change, biodiversity loss and pollution. But the European Green Deal is not just a crisis management strategy; it's first and foremost a European growth strategy.

It is important to note that the way societies receive and perceive new, transformational economical and industrial approaches is relatively slow, slower than their actual implementation. While the current pace of technological development has cycles within a single decade, the public perception and acceptance of radical transformations may require generations. Often processes that involve bio-tech processes are based on complex frontline science, which is often difficult to grasp. This can result in conspiracy theories in crises situations (such as the emergence of SARS-COV-2). It is very important that new concepts are adequately, communicated, and that the stakeholders involved (industrial entrepreneurs, scientists, funding agencies) allocate sufficient resources and design viable strategies for public information approaches about Biointelligent Manufacturing to targeted levels of society. This starts as early as in primary school, where children first learn about the manufacturing phenomenon and the resulting benefits and challenges to the environment and the economy for us all. Stakeholders need to allocate significant resources in communicating these approaches positively, highlighting them in the curriculum. This way, the increase in societal health and wellbeing via new therapeutics, food products and biocompatible industrial values are visible and tangible to all.

Cultivating an entrepreneurial spirit in society and fostering the understanding that crises are best tackled by creating new jobs, innovating and attracting new investment are crucial. For this type of approach to prevail in society, new educational policies are needed – including at the leadership level. Policies focusing on the common goal of increasing the EU's competitiveness and the well-being of its citizens. Policies that bring together national and regional EU politicians, industry, academia, business, and trade unions. Public authorities and organizations, too, have an essential role to play in promoting new quality cooperation and strengthening ecosystems.

The combination of technosphere plus biosphere can spawn an intense ethics discussion in society – a conversation that must be led by politics and result in appropriate legislation.

5.1.2. Politics

In line with the disruptive potential of Biointelligent Manufacturing – from value creation to ecological sustainability – policy makers will be challenged to create an innovation-friendly environment. This includes keeping markets free, though prudently regulated, and an open door to find investors for research and development. At the same time, politics must facilitate an open dialogue about both opportunities and risks, and actively involve all sectors of society. Countries in Europe will have to cooperate even more closely and pool their expertise to secure technological sovereignty for Europe as a macro-region.

As new opportunities for ensuring self-sustainability and securing the supply chain arise, so to do resource scarcity and global disruption of these supply chains, making self-sustainability paramount. With the integration of biological components into so many processes and products, we can harness new technologies for energy, chemicals, food, and pharmaceuticals for a start, on the road to becoming independent from external, finite resources and fossil-based precursors.

5.1.3. Technology

Newly developed technologies reflect and support the significant impact Biointelligent Manufacturing convergence will have in different domains. A new generation of products and processes – whose technological characteristics will be significantly different from previous iterations – will be invented and developed, leveraging the power of nature, engineering, and data science to solve open problems in manufacturing, mobility, energy, medicine, and agriculture.

Key innovations will rely on life science and technologies working hand in hand to overcome the traditional sequential cycle of technology readiness levels (TRLs) that have stymied innovation in recent decades. With reference to all the different examples of technologies contributing to Biointelligent Manufacturing convergence, from synthetic biology to 3D and 4D bioprinting, from soft robotics to biosensors and bioactuators, from bionetworks and DNA storage to biofuels, the strong integration among the three different domains can be truly impeded by a sequential approach to science and discovery. To counter this, multidisciplinary teams will work in parallel to research challenges iteratively targeting different TRLs will possibly substitute a mono-disciplinary and sequential approach to discovery, innovation and operationalizing results.

Several revolutionary paradigms characterise the technological evolution driven by innovation as an effect of the convergence of the three different domains. For example, the principle of diversity as an advantage, which has always been driving the evolution of nature, could be exploited in different domains of manufacturing and information technology to create a new generation of solutions that would overcome the traditional objective of variance reduction.

Similarly, life sciences will fully exploit the power of integrating "artificial" sciences with natural ones, and basic sciences with applied research. This new set of hybrid technologies will demand new methods and tools to design, fabricate, simulate, manage, monitor, control, dismiss, and recycle solutions where organic and inorganic domains are intimately integrated.

5.1.4. Economy

The industrial impact from the introduction of Biointelligent Manufacturing in the European production system has emerged clearly from analysis to date. European production capacity, and in particular the ability to produce machines and systems, is very sophisticated and well-structured. Building on this capacity, Europe could become the world's leading manufacturer of Biointelligent Manufacturing equipment. European sovereignty needs strong producers of capital goods and strong users of capital equipment, playing an active role in biointelligent transformation from the outset to avoid falling behind, as has happened in the energy sector or in computer chip production.

The Biointelligent Manufacturing transition will promote a new era of products, processes and systems that will satisfy main expectations: sustainability, efficiency and novelty of applications (Figure 5.1). The biointelligent approach can improve sustainability, thanks to its capability of reusing biomaterial in multiple lifecycles, or simply substituting non-organic resources with biomaterials with higher reuse potentials (such as the transition to organic computers, which can improve sustainability). A biointelligent approach could also encourage and inspire new types of products that are not yet imaginable with today's non-organic resources. In fact, new interaction modes between the bio- and non-bio worlds allow for new interoperable interfaces between more systems of different types – new devices that share a common border between different communication

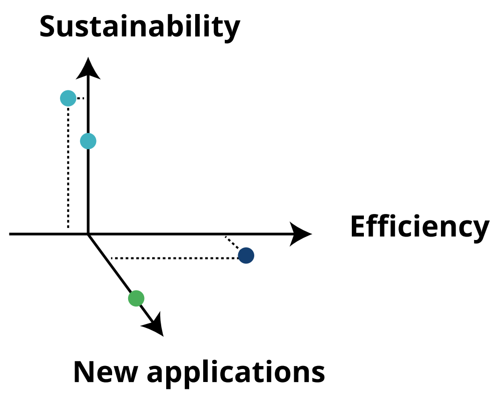


Figure 5.1 *Biointelligent Manufacturing Products Expectations*

protocols. Obviously it's plausible to think of scenarios in which the combination of at least two of the three main threads of Biointelligent Manufacturing is necessary for specific solutions. All these scenarios are subject to current technological limits and worldwide policies and economies. This is why Europe must not miss this opportunity to be part of this transition – even to drive it – in order to expand in directions that can improve the EU's internal economy and quality of life.

In the short term, it's expected that Biointelligent Manufacturing contributes to the improvement of products, adding functionalities and features, in particular in the healthcare field. This will happen, for example, with preventive medicine, where the increasing performance of labs-on-chips and organs-on-chips will contribute to improve interaction with cells in a more refined way, due to the introduction of biosensors, obtaining more information with higher precision. This means the production of personalised products with sophisticated interfaces with human beings.

In the medium term, Biointelligent Manufacturing may contribute to improving manufacturing systems and methods in terms of productivity, quality, improved human/machine cooperation, human safety, and environmental safety. Due to these improvements in manufacturing systems, new bio-products will emerge. For example, new materials will be created through the interaction between bio- and non-bio worlds. Materials can improve sustainability by exploiting the characteristics of the bio-world, ensuring higher recovery efficiency, and substantially enhancing circularity.

In the longer term, industry will create new biointelligent products for new needs. The trend will be to go beyond the needs of the individual in purely curative or improving terms. The goal will be to go beyond the existences, to expand the limits of both our body and technology. Improved information obtained from new biointelligent products and systems should not only be seen as curative information, but information that can optimise the management of the human body as a proactive medicine.

When mankind starts producing items that are both bio and non-bio with a system that is able to integrate these two types of mechanisms, a myriad of new products can emerge, far beyond our current expectations. New potential opens up to unknown domains, as with the mobile phone and then the smart phone, whose importance in covering (and creating) new human needs was not imaginable until it was created and released to the public.

There is no limit to the human imagination and reality could actually go beyond fiction. For example, infrared biosensors – cell-based sensors detecting wavelengths that human eyes cannot detect – could extend the human field of vision in real time, if these signals are integrated at the neuronal level, the brain may interpret and integrate them in the normal perception and reasoning. Even if these are somewhat frightening perspectives, they demonstrate the disruptive potential of integrating bio- and non-bio worlds through biointelligent products. They also show the importance of ethics in defining the potential impact of biointelligent revolution.

5.1.5. Legislation

In addition to acceptance by society, the biological transformation of industrial value creation will impact the demand for new and revised legal regulations and political frameworks. Standardisation will help to simplify legal regulation and control. The regulation of the use of biological or genetically modified material is very different across the globe, hindering the spread and use of innovative technology. A shift to a risk-based approach in evaluating biointelligent technologies and clear rules on containment strategies must be defined to enable implementation of biological components into manufacturing entities.

The principle of bioethics should also emerge in these discussions. This philosophy of Biointelligent Manufacturing should be carefully considered, with bioethics and sensitive topics thoroughly discussed in terms of using human tissues, health records, in vivo testing and similar techniques, which are indispensable pillars of Biointelligent Manufacturing.

5.1.6. Environment

The concept of Biointelligent Manufacturing closely follows natural processes and contributes to the concepts of bio and circular economies. It is important to emphasise that Biointelligent Manufacturing should rely on the unique environmental concepts that are paramount to circular economy, such as decoupling economic growth from the use of resources, implementation of circular material flows among regional industries, etc.

Biointelligent Manufacturing relies on the deeper involvement of in silico simulations of natural processes, which aims at the replacement of in vivo (and to some extend in vitro and in chimico) methods. The digital simulation of complex biological processes by supercomputing aims to reduce resource-inefficient industrial processes, such as material and energy use. In that respect, decarbonisation targets may be easier to achieve. Biointelligent Manufacturing industries will rely on the use of renewable energies, while raw materials should avoid fossil-based precursors. Circular material flows should be ensured. Only in this way can we increase production capacity of bio-based raw materials, which can gradually replace fossil-based ones and provide sustainable supply chains for the entire cycle of production.

5.2. Scope of Biointelligent Manufacturing

Given the impact on a variety of stakeholders, biological transformation of industrial value creation requires a multitude of developments in all areas: from research and development; through industrial applications and business models; to new concepts for education and training. Furthermore, synergies and collaboration between different building blocks becomes increasingly important. Equally, cross-spanning questions, such as standardisation and harmonisation or the careful and quantitative assessment of social and environmental impact, is gaining increased attention.

Several key research areas and action points have been identified to harbour core enabling technologies. Those developments will be needed to enable Biointelligent Manufacturing.

These findings are not all unique to Biointelligent Manufacturing, but account for different areas of future manufacturing. In order to achieve its goals, the Manu*FUTURE* Vision 2030 has already defined three major building blocks:

- science and technology,
- innovation and entrepreneurship,
- education and training.

Building on these blocks, the following chapters provide more details for successful Biointelligent Manufacturing IMPLEMENTATION in Europe through innovation and development in these three areas.

6. Research and Technology Development

6.1. Technology Convergence as Driver for Knowledge Creation

Convergence among different technologies is currently one of the main drivers of knowledge creation in the related scientific domains. Lowering the boundaries of access to knowledge and planning for a more conscious exploration of the frontiers of innovation is one key ingredient of research and innovation. Among the most relevant drivers: the hybridisation of industrial and information technologies with life sciences and cognitive sciences, creating different perspectives and combining organic and inorganic sciences with digital manufacturing. This convergence is currently driving several dimensions of scientific research and innovation development.

Studies on technology foresight highlight this hybridisation as a central element predicting wide-reaching societal impact. Figure 6.1 summarises a subset of disruptive technologies predicted to drive the global challenges in the near future. In this diagram, the convergence between biology and biotechnologies, between manufacturing and digital intelligent solutions is playing a main role as an engine for future research and development (source: Technology foresight of Imperial College, Fraunhofer and Politecnico di Milano).[20]

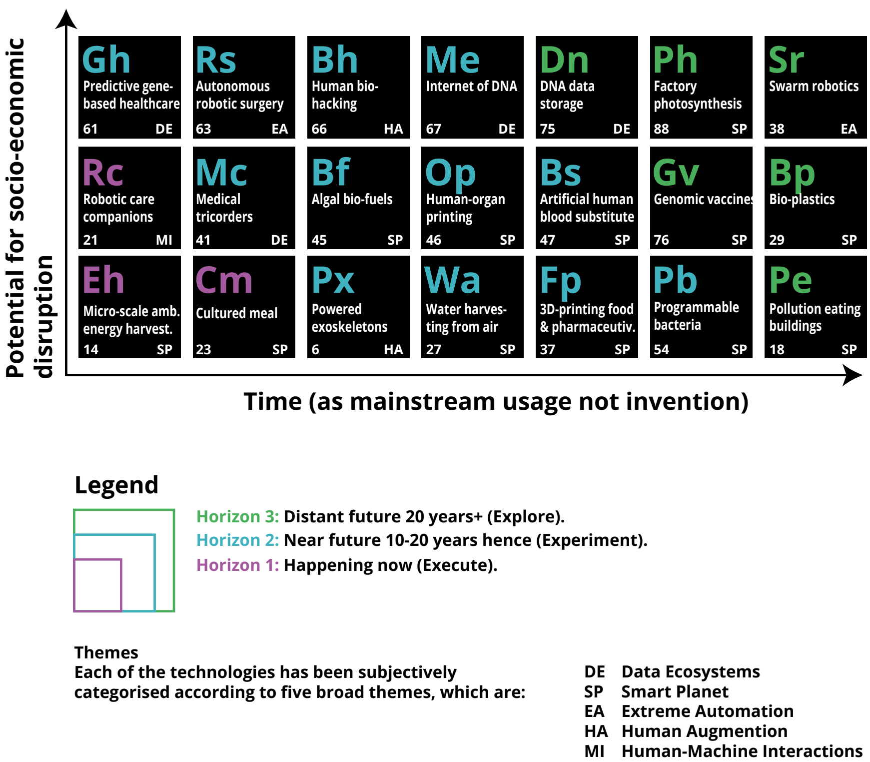


Figure 6.1 *Biointelligent Manufacturing in technology foresight (adapted with permission from: Tech Foresight; reference: https://imperialtechforesight.com/visions/table-of-disruptive-technologies-2/)*

In Figure 6.1, the disruptive technologies are associated with a specific theme, listed in each box on the bottom right corner, namely: DE: Data Ecosystem; SP: Smart Planet; EAS: Extreme Automation; HA: Human Augmentation; MI: Human-Machine Interaction. In the technology foresight study from Imperial College, most of the disruptive technologies that are related to the Biointelligent Manufacturing shift are also highlighted as impacting the green transition, since they are mainly associated with the "SP" (i.e., SMART PLANET) macrotheme. Examples of products based on these disruptive biointelligent technologies, impacting the future of our planet, are:

1. Large-scale cell cultures, replacing animal farms, resulting in, e.g., cultured meat
2. Micro-scale ambient energy harvesting, e.g. in biomedical implants
3. 3D printing of food, pharma and tissue products
4. Artificial human blood substitutes
5. Programmable microbes
6. Algal high end products and other biotechnologically produced feeds, foods and fine chemicals
7. Novel bioplastics
8. Microbial cement and other inorganic materials
9. Photosynthetic biofactories
10. Genomic vaccines
11. Pollution neutralising surfaces and buildings

20 https://imperialtechforesight.com/visions/table-of-disruptive-technologies-2/
https://www.foresight.polimi.it/

All technologies and innovations identified as disruptive in the next 10 to 20 years are strongly linked with the Sustainable Development Goals (SDGs) adopted by all United Nations Members States, as shown in Figure 6.2.

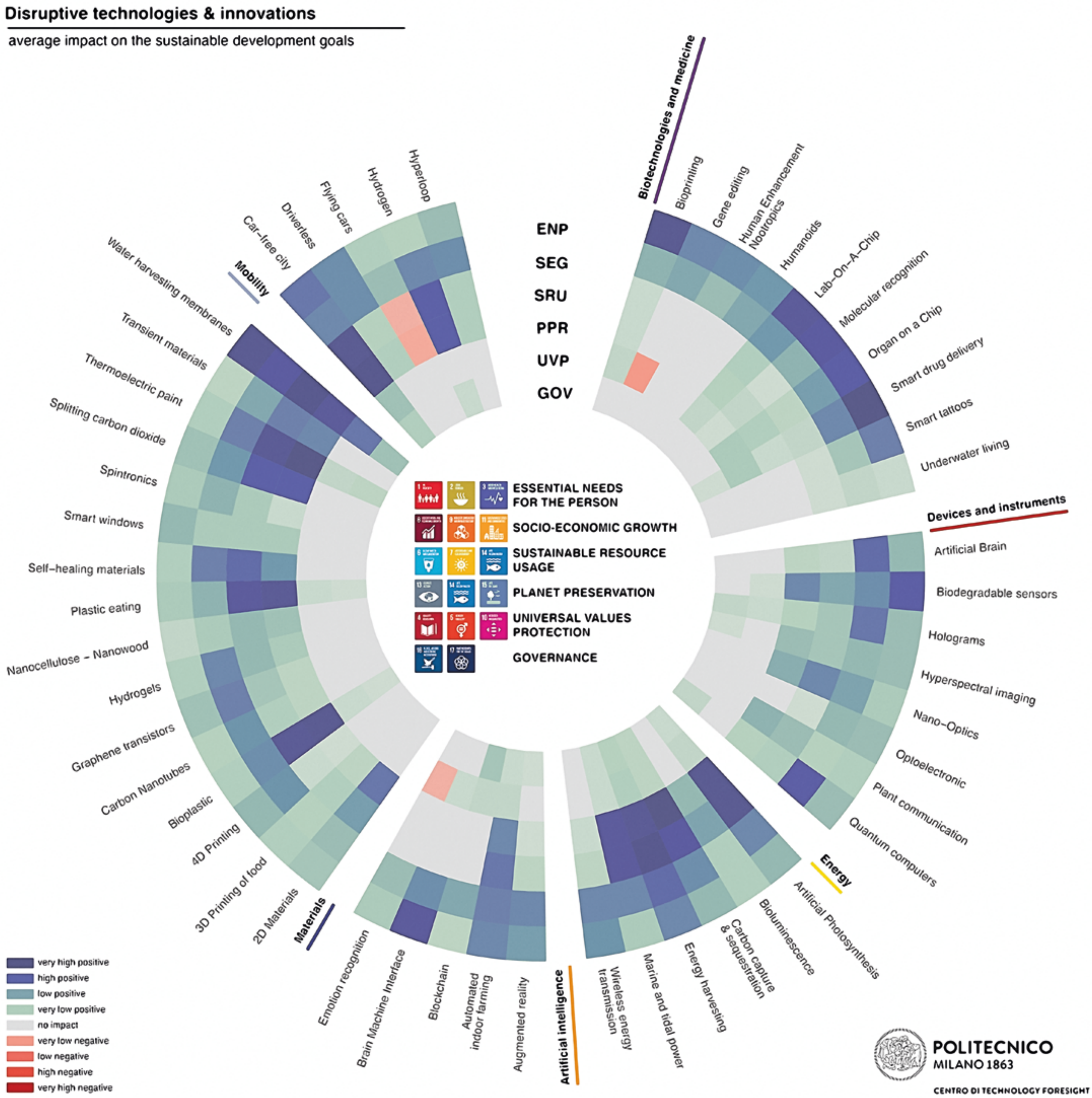


Figure 6.2 *Link between disruptive technologies and sustainable goals (Politecnico di Milano – technology foresight)*

A similar analysis of production in scientific journals in the last five years clearly highlights how Biointelligent Manufacturing convergence provides relevant and fast-changing research guidance, identifying where impactful results can be achieved in the coming years. Figure 6.3 shows a "prominence map", where "prominence" is the indicator defined in Scopus-SciVal to compute the momentum gained by a specific research topic in recent years.[21] (source: scopus – Scival). This graphic map for the most prominent topics provides an identity card for the research topics of greatest impact in the reference period on a given topic. In the prominence map, every bubble in the chart represents a research topic, the size of the bubble indicates the number of publications on that topic in the period of reference, and the bubble's position is linked to the area where it belongs (computer science, chemistry, mathematics and physics, engineering, energy and biology, medicine, and social sciences).

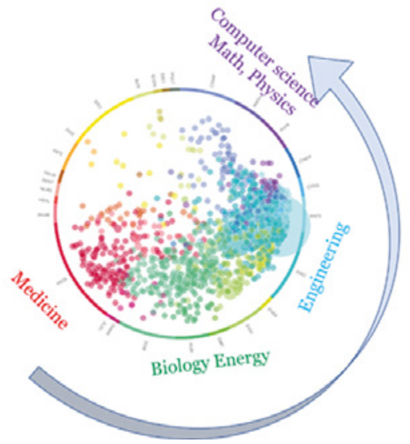


Figure 6.3 *Scopus prominence map of scientific production in the last five years considering "Bio" AND "manufacturing" as keywords in the query – (last update – Feb 2022)*

Interestingly, the distance of each bubble from the outside circle is an indication of interdisciplinarity of each research topic: as is clear from the prominence map, a significant number of high-prominence topics consider interdisciplinarity as a key factor, since they are located close to the centre of the prominence map. Another element of the prominence analysis, the word cloud shown in Figure 6.4, presents a summary of relevant keywords in the last five years' of literature on Bio and Manufacturing. In this word cloud, the size of the keyword refers to the relevance of the specific word in scientific literature and the colour is used to highlight topics that are increasing (green) or decreasing (blue) their importance. It's not surprising that all keywords in the word cloud on bio and manufacturing are green, showing an overall increase of relevance of these topics in scientific production.

6.2. Open Challenges for Biointelligent Manufacturing

Various open challenges should be mentioned as characterising the overall scenario of research and innovation for a future of Biointelligent Manufacturing.

The first element of action concerns the interface among the different domains, which define novel approaches and paradigm shifts for interface integration. In the field of Biointelligent Manufacturing many different interfaces need to be merged and

Figure 6.4 *Word cloud of key-phrases in scientific production in the last five years considering "bio" AND "manufacturing" as keywords in the query – (last update – Feb 2022)*

21 Gerald Byrne, Dimitri Dimitrov, Laszlo Monostori, Roberto Teti, Fred van Houten, Rafi Wertheim, Biologicalisation: Biological transformation in manufacturing, CIRP Journal of Manufacturing Science and Technology, 2018, 21,1-32, https://doi.org/10.1016/j.cirpj.2018.03.003.

integrated: the organic/inorganic interface; the sensing/actuating functionality; the passive/active role enabled by the embedded intelligence and digital capability. Novel approaches to reshape the interface and to interrelate the different domains is likely to create several research challenges in fostering convergence among the different applicative domains.

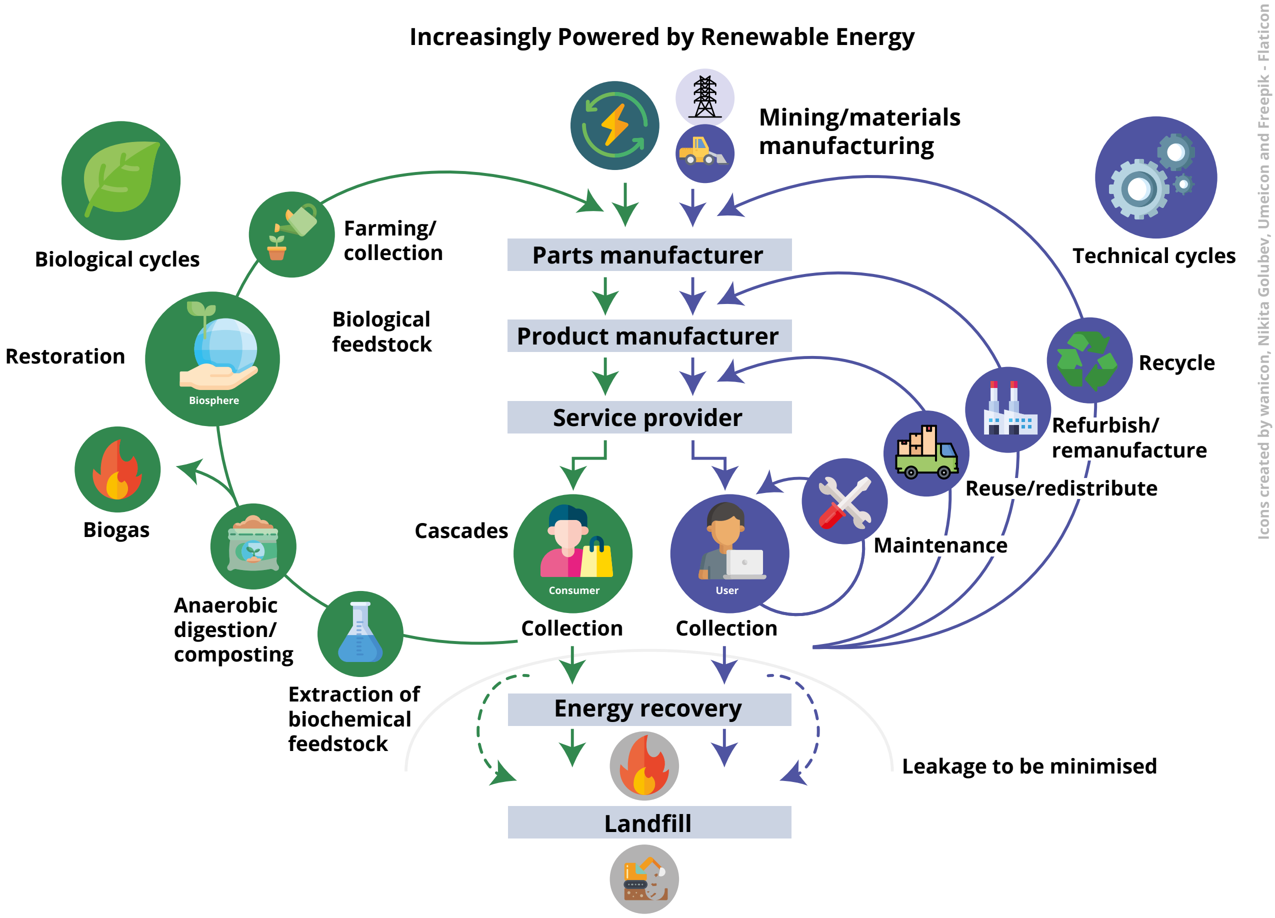


Figure 6.5 *Circular economy (with permission from: Anthony Halog; reference: HALOG, Anthony; ANIEKE, Sandra. A review of circular economy studies in developed countries and its potential adoption in developing countries. Circular Economy and Sustainability, 2021, 1.1: 209-230. A Review of Circular Economy Studies in Developed Countries and Its Potential Adoption in Developing Countries | SpringerLink)*

A second challenge is represented by solution methods and tools to manage a significant amount of extra variability and a significant dynamical behaviour due to the introduction of natural and organic elements into the manufacturing cycle. Biological entities, such as living cells or biomaterials, introduce a significant change in the amount of part-to-part, batch-to-batch and time-to-time variability that has to be considered at the design and manufacturing stages. In this scenario, the intelligence contribution should be appropriately designed to let the system gain self-adapting and self-tuning capabilities, enabling a paradigm shift from serial to adaptive production. Quality should be revised as a dynamic and tuneable capability of fitting the specific use. Lifetime monitoring and control, adaptive

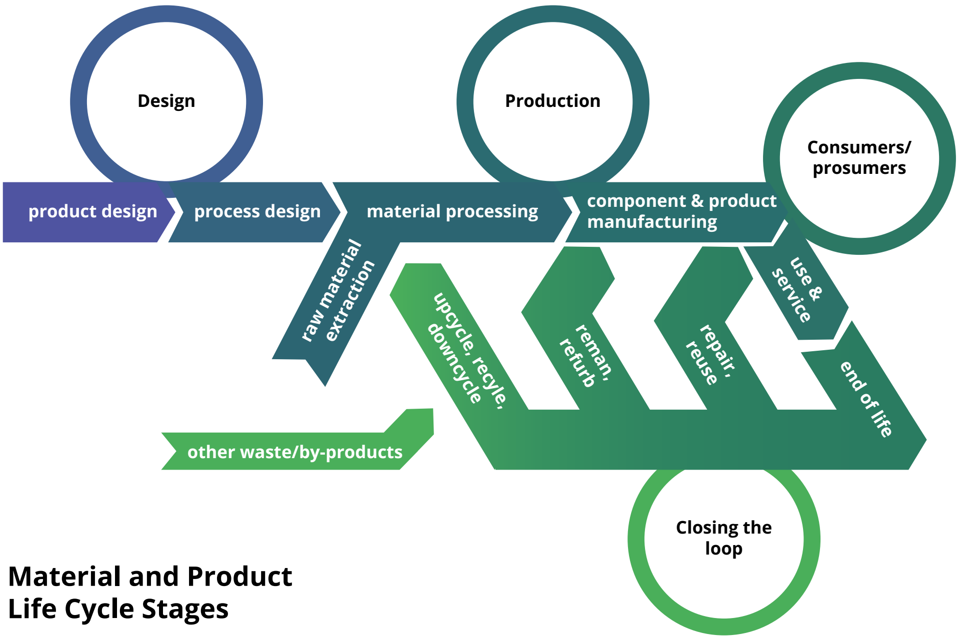


Figure 6.6 *Lifecycle adaption (with permission from: Simon Ford; reference: FORD, Simon; DESPEISSE, Mélanie. Additive manufacturing and sustainability: an exploratory study of the advantages and challenges. Journal of cleaner Production, 2016, 137: 1573-1587. Additive manufacturing and sustainability: an exploratory study of the advantages and challenges – ScienceDirect)*

maintenance, and end-of-life reuse should be further expanded to face the natural evolution of biointelligent systems.

Finally, a last driver of research and innovation should be scaling up: from low- to large volume; from lab to non-lab environment (biological products); from early stage to mature assessment in an integrated framework able to handle different readiness levels in an comprehensive vision.

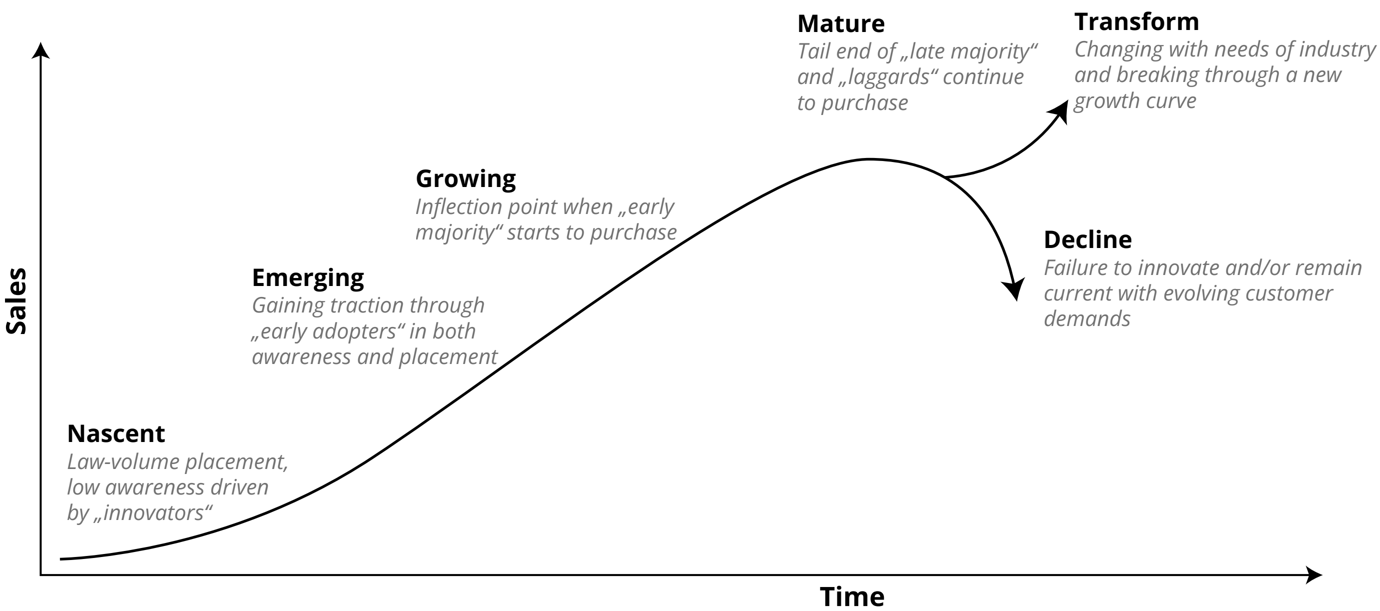


Figure 6.7 *Scaling up (with permission from: MKA Insights; reference: Frameworks and Strategies for Commercialization Success in the Biopharmaceutical Ecosystem – BioProcess InternationalBioProcess International (bioprocessintl.com))*

6.3. Core Enabling Technologies

Through analysis of the proposed topics, several possible core enabling technologies emerged that are well focused with the highlighted paradigms of the sub-platform Biointelligent Manufacturing: technologies capable of improving and innovating processes, while at the same time increasing the commercial value of products in each industrial sector, producing a systemic, competitive advantage for scientific and industrial research and employment in the near future.

The issues and related technologies identified will help the industrial world to guide European economic development in the transition from artificial to biological, focusing on competition based on research and the development of new high-tech products, the qualification of humans, and the improvement of living conditions.

Biointelligent Manufacturing draws from the interdisciplinarity of sciences and technology, where integration of cutting-edge know-how brings great additive value for Biointelligent Manufacturing and even creates new SciTech domains.

Even today, several important fields of technologies exist that play a pivotal role for the realization of Biointelligent Manufacturing.

It has been shown how enabling technologies are developing and shaping manufacturing possibilities. Goal-setting and making a collective and concerted effort towards Biointelligent Manufacturing would increase the speed of development and creation of cutting-edge manufacturing solutions for our health and sustainable industrial activities.

1. **Biosensors**
   A new class of biosensors interacting with the living organs and brains (including human) will conceivably change the way micro and nano-manufacturing is combined with biomaterial science and bioprinting to create a new class of solutions.

2. **Bionics for Machinery**
   Biorobots (pharmaceutical manufacturing, agricultural applications), bionic thinking and bionic elements for machinery, soft robots, smart biomanufacturing devices, biomimetics.

3. **Bioengineering**
   Biology contains enormous amounts of intelligence that is constantly evolving. We have come to the point that this intelligence, the biological mechanisms, responsiveness and diverse functions, can now be dissected, combined, and re-designed at our will. Or we can even pose them for evolution in the laboratory. The systems can replenish themselves and multiply, they can be dormant and response to changing environment, and they have molecular memory. Biomanufacturing can provide us fuels, chemicals, drugs, and materials. Cellular agriculture can make “eggs without chicken” and “food without fields”. Bioengineering can lead to precision deposition on materials (living 3D/4D printing), self-healing materials, or soft living robots that can enter difficult environments and be programmed to perform tasks upon stimuli. Synthetic biology can manufacture, in principle, anything nature has developed – and beyond.

4. **Digital Twins**
   Biointelligent Manufacturing relies on the deeper involvement of in silico simulations of combined artificial and natural processes which aim at the replacement of in vivo (and to some extend in vitro and in chimico) methods. Digital simulation of complex biological processes through supercomputing should aim at reducing resource-inefficient industrial processes such as material and energy use, potentially making decarbonization targets easier to achieve. The understanding of the function of genes and biological molecules is rapidly expanding, making it possible to describe biological rules and molecules ina digital form and experiment with simulated biological systems. Molecular interactions, cell compartments, entire cells and communities of cells, and even ecology can be modelled. In the future, quantum computing enables the use of huge datasets and simulation of novel molecular interdependencies and hierarchies based on the basic rules of physics, chemistry and biology. The in silico bioworld will continue to evolve and forms its own scientific domain.

   Importantly, the outcome of the simulations of in silico biology can also be realised in real-life. Synthetic biology will pave the way for radical ways to engineering biology. This creates novel concepts and ways of manufacturing using biological principles and cells, combined with autonomous process control. This Biointelligent Manufacturing enables the production of new chemicals, novel responsive, and intelligent materials, precision drugs, and sensor-actuators that make use of the high specificity of biomolecules and their coupling to biological logic gates and circuitries.

5. **Micro- and Nanomanufacturing**
   Materials and strategies for micro manufacturing, the use of biointegration for new generation of textiles for clothes, bioinspired materials/production, bioinspired lightweight production, flexible micro manufacturing, hybrid micro manufacturing.

6. **Additive Manufacturing, Bioprinting and 4D Printing**
   AM will play a significant role for fabricating complex shapes using biomaterials, hydrogels printing in soft-robotics, bioprinting of tissues and organs, microfluidic devices and lab on chips.

7. **Bioactuators**
   For about 15 years, applied research has tried to simulate bioactuators with carbon nanotubes, electroactive polymers, and other controllable materials. Now, science has started to employ muscular cells directly to compose biotechnical actuators.

8. **Lab-on-a-chip Systems**
   Chemical and biochemical processes can be set up and controlled in decreasing size, approaching dimensions of natural regulatory systems. In the future, this will not only be used as micro and nano labs in science, but to utilise controlled processes for productive measures, too.

9. **Cradle-to-cradle Concepts**
   The Biointelligent Manufacturing industries should rely on the utilisation of renewable energy; raw materials should also avoid fossil-based precursors. Circular material flows should be ensured to allow increasing the capacity of production of biobased raw materials, which can gradually replace fossil-based ones, providing sustainable supply chains for the entire cycle of production.

7. Industrial Applications and Business Models

7.1. Biointelligent Manufacturing as a New Concept of Product Transformation

Biointelligent Manufacturing can be thought of as a new approach to the concept of manufacturing – or as a new way of conceiving the processes of transforming incoming materials and/or products that can be bio and non-bio. and then get new products or materials both bio and non-bio, as seen in the previous chapter. Clearly, this transformation is only possible if the two worlds come together to implement this new concept: the bio/organic world – strongly focused on the concept of continuous production (cells, materials, etc.) – and the discrete world, strongly oriented towards the production of goods. What we expect to emerge from this integration is an approach to a production system strongly focused on discrete manufacturing, because the interaction of the bio and non-bio worlds has the purpose of developing new products – or innovative products for which the material (cells or organic material in general) is one of the vehicles through which transformation takes effect.

Therefore we need to focus on the research and development of new strategies of discrete manufacturing that allow us to conceive new methodologies of interaction between the two worlds to achieve both new products and processes, but also new machines capable of interacting with these two worlds.

Such a vision would lead to a paradigm shift towards new production purposes and, consequently, to an expansion towards new markets of which Europe, with an important investment in terms of budget for research and development, could become one of the major players in this new form of discrete manufacturing. These new technologies and new ways of conceiving the integration between different production methods could open up the creation of products never imagined before, which could be able to extend the cognitive capacities of mankind.

Let's think, for example, of the disruptive effect that smartphone technology has had. No one could have imagined what kind of communications would have arisen without investing in this new technology. Looking at the image below (Figure 7.1), it emerges how important the investments in research aimed at the development of these devices have been. Let's think for a minute about the evolution of the cameras integrated into these devices. It started with a simple low-resolution camera up and quickly evolved into pocket-sized, multi-camera systems which have opened up new features unimaginable until now.

The smartphone increased the potential of human beings so much as to become an indispensable tool. Not only is a technological aid, but it has a social impact. Indeed, it has expanded the concept of sociality dramatically, making it possible to get in touch with anyone, anywhere, at any time, reducing the distance between people. The graph in Figure 7.2 below shows the diffusion curve of smartphones over the last 15 years. A comparison with the previous graph [Figure 7.1], shows that technology had a slowly growing market penetration at the time of the research phase, initially from 2000 to 2007, which then led to a phase of product diffusion, thanks to industrial maturity, between 2007 and 2013.

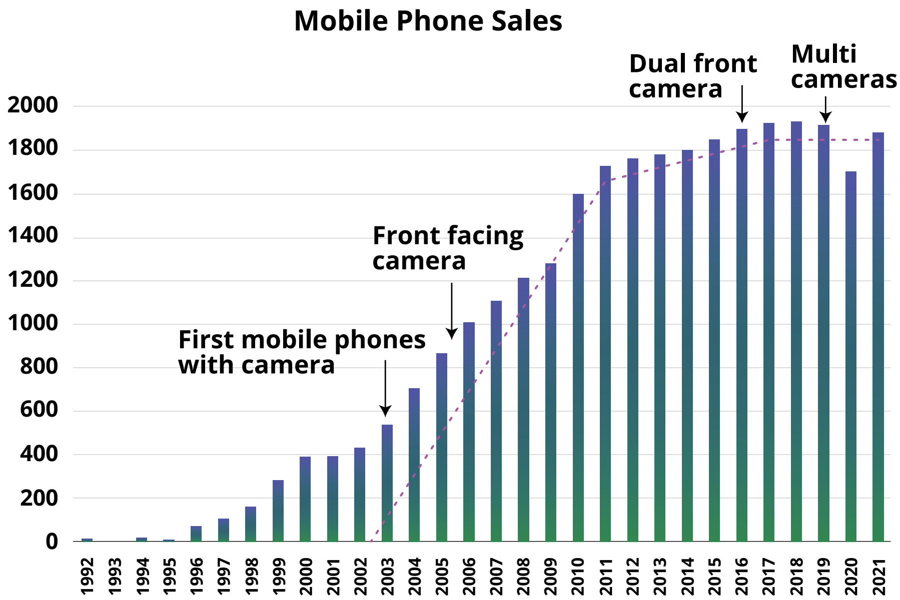


Figure 7.1 *Worldwide smartphone and feature phone sales with breakdown of suppliers (source: Gartner reported in Blahnik, Vladan and Schindelbeck, Oliver. „Smartphone imaging technology and its applications" Advanced Optical Technologies, vol. 10, no. 3, 2021, pp. 145-232. https://doi.org/10.1515/aot-2021-0023)*

Similarly, Biointelligent Manufacturing can have an enormous impact on our societies. Devices which were unconceivable even a few years ago become possible. These devices can create a new standard of living by improving human health or increasing human capabilities. They will become indispensable once humanity adapts to them. Additionally, it creates new ways of production: improving efficacy, efficiency and sustainability. Therefore, Biointelligent Manufacturing will, in all likelihood, become an inseparable companion to humankind.

Potentially, each person might need several biointelligent devices and any company will have some Biointelligent Manufacturing process. Therefore, growth potential is extremely high. But we must invest in now to reap the benefits of high production volumes in the future, and position Europe as the leader in both the technologies and in products of Biointelligent Manufacturing.

Think back to another disruptive technology, electronic chips. Europe discovered at great expense how critical is to lead at the beginning of a new era. We're still trying – with an enormous investment in the chips act – to get back to 20 % (!) of the market share we could easily have attained if Europe had invested more consistently during the beginning and the raising phase of the technology. From this we know it is very important to recognise not only the huge potential of Biointelligent Manufacturing, but also the fact that the number of Biointelligent Manufacturing devices will grow rapidly. Those parts of the world that invested early have acquired an enormous competitive advantage, which is almost impossible to compensate for with late investment. Therefore, the time to act is now, and our collective actions should be beyond sufficient to position Europe as being in the driver's seat on building Biointelligent Manufacturing.

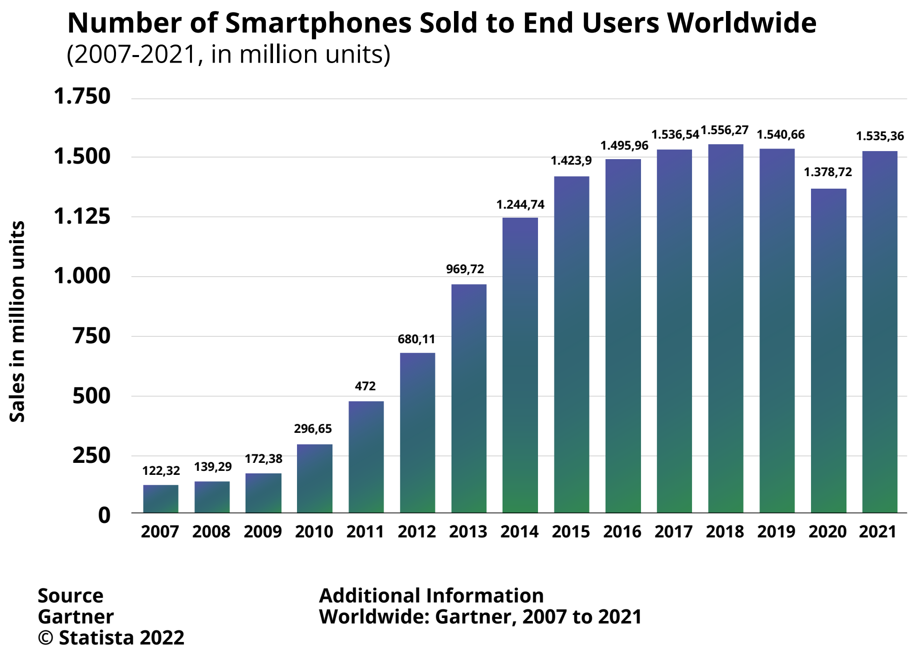


Figure 7.2 *Smartphone penetration as a share of the population in the United States from 2010 to 2021. In 2018, 69.6 % of the U.S. population used a smartphone. (Source: Gartner reported in "Smartphone penetration in the U.S. as share of population 2010-2021" Published by S. O'Dea, Apr 8, 2020)*

7.2. Industrial Applications of Biointelligent Manufacturing

The areas of action of Biointelligent Manufacturing have been introduced broadly in clause 4.2 with Figure 4.3. It emerges clearly from previous analysis that 3 out of 4 of the defined context areas are generally involved in Biointelligent Manufacturing.

The purpose of this clause is to associate, from the point of view of industrial impact, the phases characterising various technologies identified as clear examples of Biointelligent Manufacturing, compared to the quadrants of the field of action introduced in Figure 4.3.

Therefore, some examples of industrial applications, both in terms of processes/systems and product, have been analysed trying to identify their interactions within the fields of actions of Biointelligent Manufacturing as recapitulated in Figure 7.3.

The following paradigms of Biointelligent Manufacturing will be elaborated (Figure 7.4):

1. Observing biological to replicate on artificial
2. Using biological in combination with artificial
3. Using biological to create artificial
4. Using artificial to create/operate on biological
5. Using artificial to substitute biological

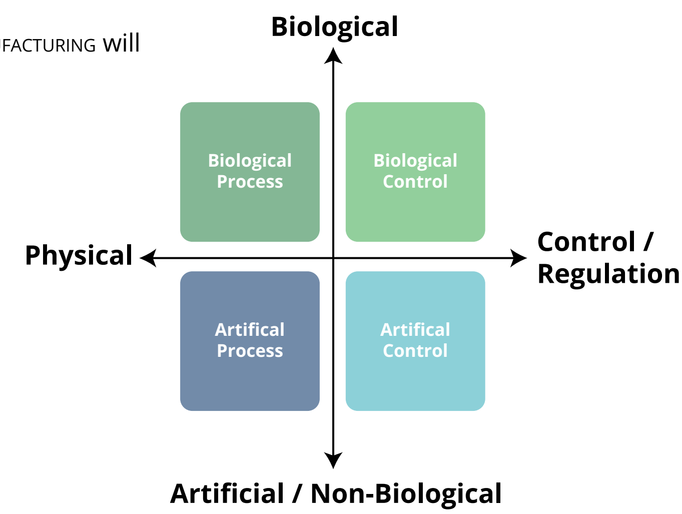


Figure 7.3 *Topology overview of Biointelligent Manufacturing*

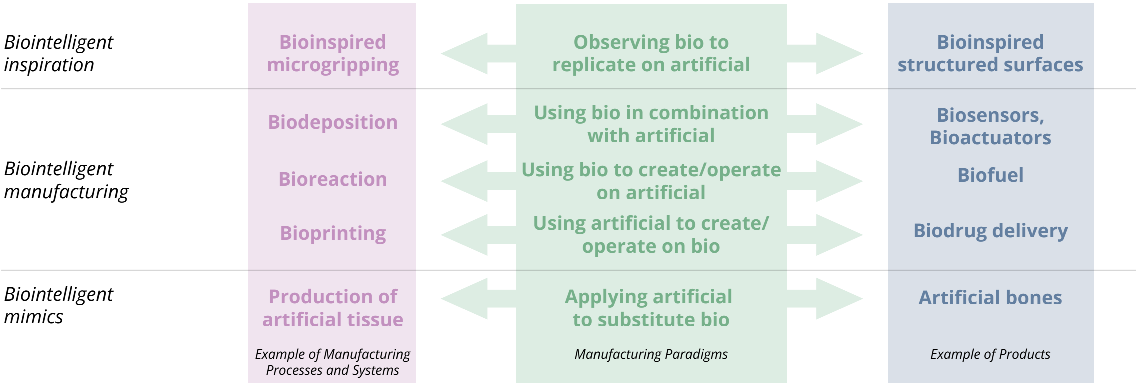


Figure 7.4 *Description of different paradigms of Biointelligent Manufacturing*

1. **Observing biological to replicate on artificial:** this paradigm considers one of the oldest approaches to nature observation: to observe how nature has adapted itself to the environment in order to survive. Artificial membranes are a clear example of the application of butterfly wings' hydrophobicity. Another example are mini "row-bots" that use slender legs – like water insects – to exploit the surface tension of water. Other examples of Manufacturing Processes and Products are reported below:

   - Manufacturing processes: molecular machines; self-organization; bioprinting; towards 4D printing to create structures that change over time as biological organism; deep learning; neuromorphic computing; create models of intelligence at different factory levels (new machine/structure/new level of multi machine cooperation); and the basic concept of Industry 4.0, to distribute intelligence while enhancing the communication between the entities.

   - Products: hydrophobic and hydrophilic surfaces; bionics; soft robots; nanostructured coatings using bio patterns, lightweight products; self-healing devices; bioinspired tissues and materials in general.

   The typical process followed by observing biological to replicate on artificial is reported in Figure 7.5 with the help of the four quadrants of the field of action of Biointelligent Manufacturing (Figure 7.3) for the case of microgripping.

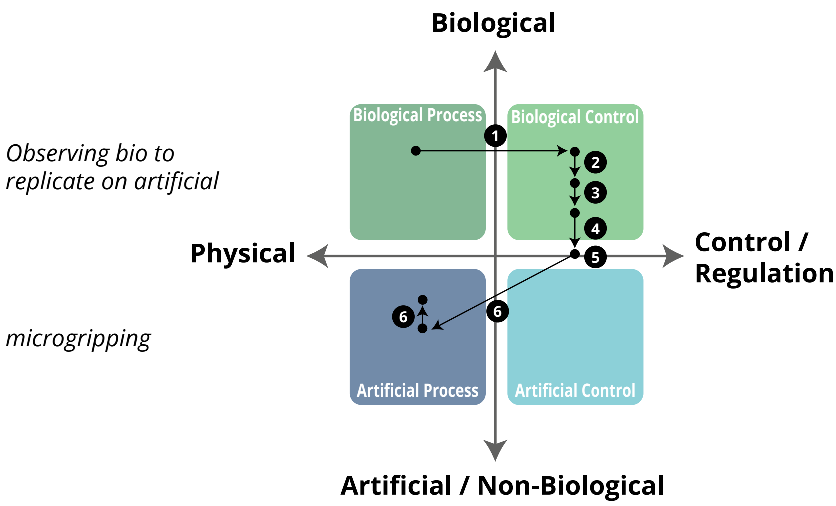


Figure 7.5 *Logic sequence in the field of action of Biointelligent Manufacturing for the process microgripping, as an example of the paradigm Observing bio to replicate on artificial: 1. observation and conceptualization; 2. explore potential applications; 3. select an application; 4. design application; 5. design microgripper; 6. produce microgripper; 6. apply microgripper for the scope*

Another example is the „bioinspired structured surfaces“ (Figure 7.6) whose possible applications are reported in the Gartner Hype Cycle related to surface materials and treatments.[22]

Observing bio to replicate on artificial

microgripping

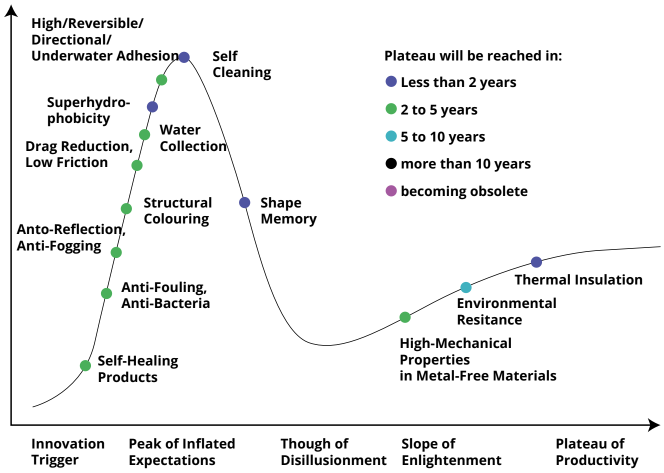


Figure 7.6 *Gartner Hype Cycle for applications and expectations for materials and surface treatments.*[23]

Considering the processes, an example is surface adhesion microgripping (Figure 7.5), which exploits the principle of the skin adhesion to objects in order to be able to precisely pick and release micro components.

2. **Using biological in combination with artificial:** This paradigm focuses on solving specific problems where nature and artificial coexist. This may mean, on the one hand, that a cooperative interaction is sought or, on the other hand, that the interaction needs to be prevented. An example of this paradigm is the artificially controlled usage of enzymes to purify wastewater. Another example is the introduction of artificial barriers to avoid contamination or biodegradation. Other examples of manufacturing processes and products are reported below:

   a. **Manufacturing processes**: preventing contamination in manufacturing sites; enzymatic recycling in a bioreactor; preventing contamination of products; bio-computer interfaces.

   b. **Products**: organ on chips; hybrid actuation; multifunctional bio-sensor chips; biointelligent food quality monitoring; combine natural cells with synthetic material; green construction material; biointelligent facades.

22 Gerald Byrne, Dimitri Dimitrov, Laszlo Monostori, Roberto Teti, Fred van Houten, Rafi Wertheim, Biologicalisation: Biological transformation in manufacturing, CIRP Journal of Manufacturing Science and Technology, 2018, 21,1-32, https://doi.org/10.1016/j.cirpj.2018.03.003.

23 Fußnote fehlt

The typical process followed by using biological in combination with artificial is reported in Figure 7.7 with the help of the field of action's four quadrants of Biointelligent Manufacturing (Figure 7.3) for the case of biodeposition on cracks of concrete. The idea of this process is to fix cracks in concrete by using the action of Ureolytic bacteria such as Bacillus sphaericus that can precipitate $CaCO_3$ in their micro-environment by conversion of urea into ammonium and carbonate. The bacterial degradation of urea locally increases the pH and promotes the microbial deposition of carbonate as calcium carbonate in a calcium-rich environment. These precipitated crystals can thus fill the cracks.[24]

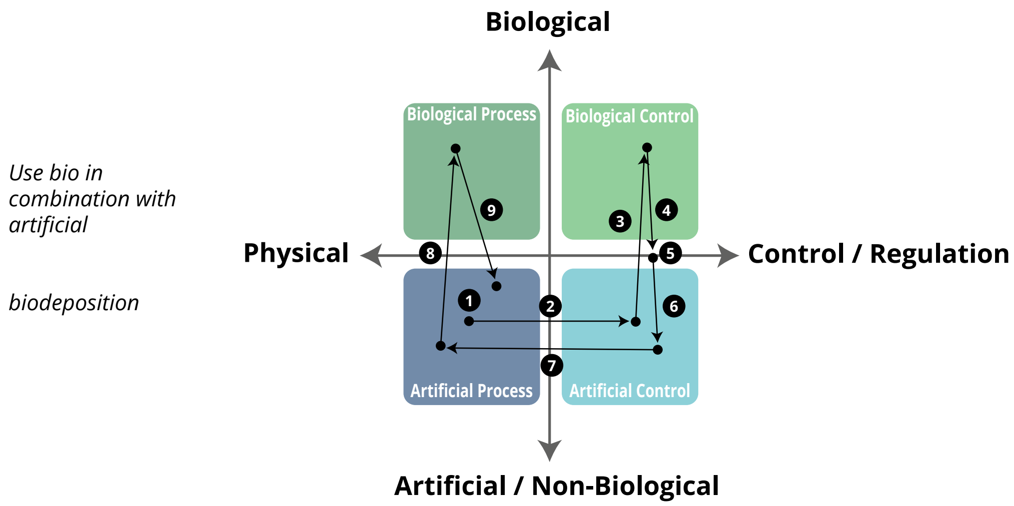


Figure 7.7 *Logic sequence in the field of action of Biointelligent Manufacturing for the process Biodeposition on cracks of conrete material, as an example of the paradigm Using bio in combination with artificial: 1. damaged concrete; 2. data acquisition; 3. analysis of concrete damage; 4. define strategy; 5. process modelling; 6. process definition; 7. download program; 8. position cells; 8. cells activation.*

3. **Using biological to create artificial:** This paradigm uses the characteristics of biological organisms or processes suitable for creating artificial products, such as enzymes in digesters for the production of biogas or for the transformation of waste plastic into biofuel. Other examples of manufacturing processes and products are reported below:

   a. **Manufacturing processes:** food production (e.g., leavening); biobased recycling processes; bacteria for sorting inorganic waste; biomass fermentation; synthetic biology; artificial photosynthesis; production of drugs with bacteria.

   b. **Products:** biobased drugs; DNA-based data storage; biofuels; biogas.

   Figure 7.8 presents the logic sequence, inspired by the fields of action of Figure 7.3, of an example from process industries responding to this paradigm: bioreactors for waste material used to produce biofuel.

24 DE BELIE, Nele; DE MUYNCK, Willem. Crack repair in concrete using biodeposition. In: Proceedings of the International Conference on Concrete Repair, Rehabilitation and Retrofitting (ICCRRR), Cape Town, South Africa. 2008. p. 291-292.

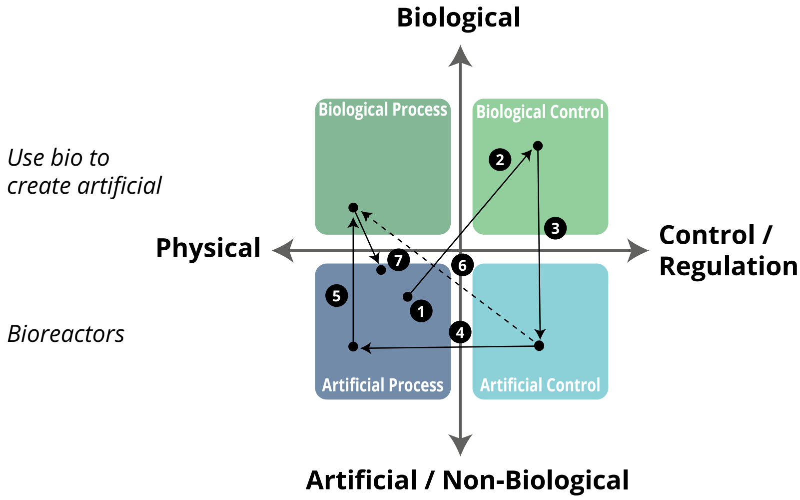


Figure 7.8 *Logic sequence in the field of action of Biointelligent Manufacturing for the process Bioreactors for waste material, as an example of the paradigm Using bio to create artificial: 1. identify products; 2. analysis of possible treatments; 3. process treatment design; 4.process implementation; 5. loading bioreactor; 6. bioreactor control; 7. biofuel production*

4. **Using artificial to create/operate on biological:** This paradigm focuses on an inverse approach, from the observation of nature and biological world, in particular, biological mechanisms can be identified on which to operate with an artificial action. The drug identifies this contribution of the artificial to the biological world. However, the action of drugs is often widespread while technology is trying to create much more targeted applications, such as the injection of localised microcapsules with programmed absorption for local efficacy or minimally invasive cancer surgery such as cauterization of tumour tissues with hot needles. Other examples of Manufacturing Processes and Products are reported below:

   a. **Manufacturing processes:** 3D printing of pills/tablets with active substrates; bioprinting of drugs; cross contamination/free production/loading; multi-material bioprinting; sterile and clean production; tissue production; cell growth differentiation in bioreactors;

   b. **Products:** biosmart materials; bioprinters, new bionics; new cosmetics.

   The typical processes followed by using artificial to create/operate on bio are reported in Figure 7.9 and Figure 7.10, with the help of the four quadrants of the field of action of Biointelligent Manufacturing (Figure 7.3), for the case of bioprinting and lab-on-chip.

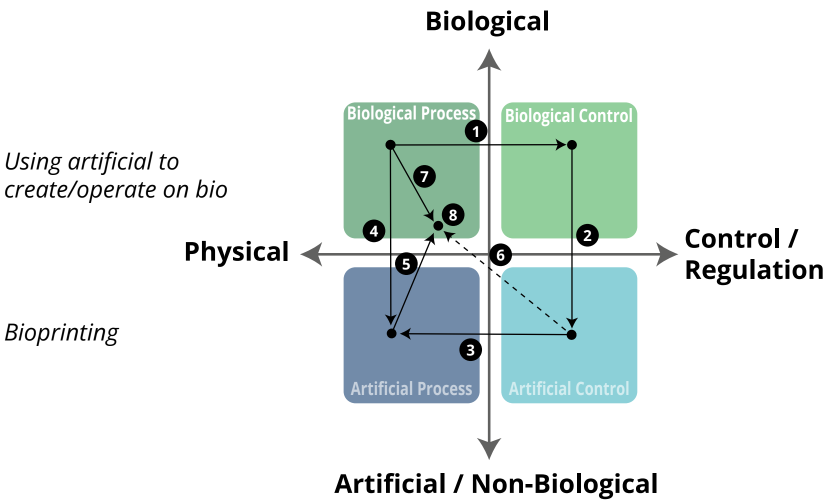


Figure 7.9 *Logic sequence in the field of action of Biointelligent Manufacturing for the process Bioprinting, as an example of the paradigm Using artificial to create/operate on bio: 1. analyse problem; 2. process design; 3. process implementation; 4. characterisation of biomaterial substrate; 5. deposition of biomaterial on substrate; 6. AI control; 7. substrate for deposition; 8. tissue*

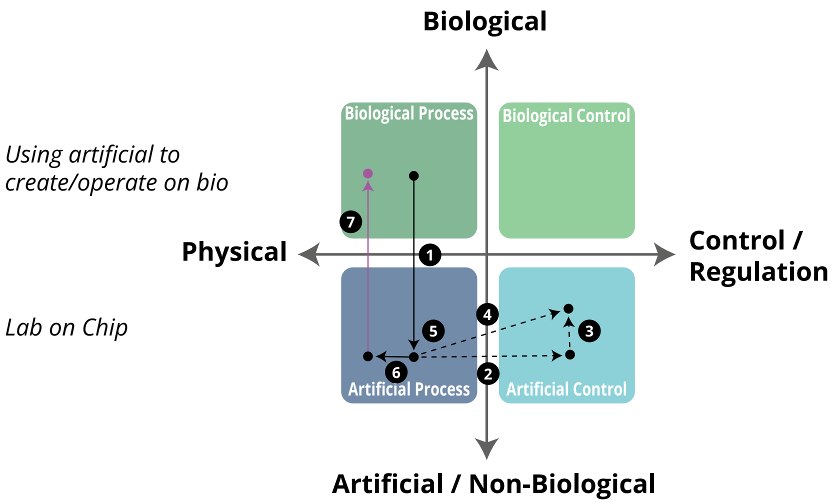


Figure 7.10 *Logic sequence for Lab on Chip operations: 1. bring biomaterial into lab on chip; 2. analysis with sensors; 3. control algorithm execution; 4. controls; 5. Lab on Chip processing; 6. unload Lab on chip; (7. release modified cells)*

5. **Using artificial to substitute biological:** this paradigm focuses on the artificial replacement of damaged biological parts. In this context, prostheses are the prominent example, but with a view to technological development, stem cells will be the defining element of this paradigm. Other examples of manufacturing processes and products are reported below:

   a. **Manufacturing processes:** bioprinting for replicated human body (antibodies); use bioprinting tissue to test new elements in cosmetic industries; food production;

   b. **Products:** biosmart materials; customised 3D printed implants; implement vascularisation in 3D bioprinted tissue and organ models; tissue engineering; regenerative medicine; organs transplantation.

   The typical process followed by artificial to substitute biological is reported in Figure 7.11 with the help of the four quadrants of the field of action of Biointelligent Manufacturing (Figure 7.3), for the case of tissue synthesis.

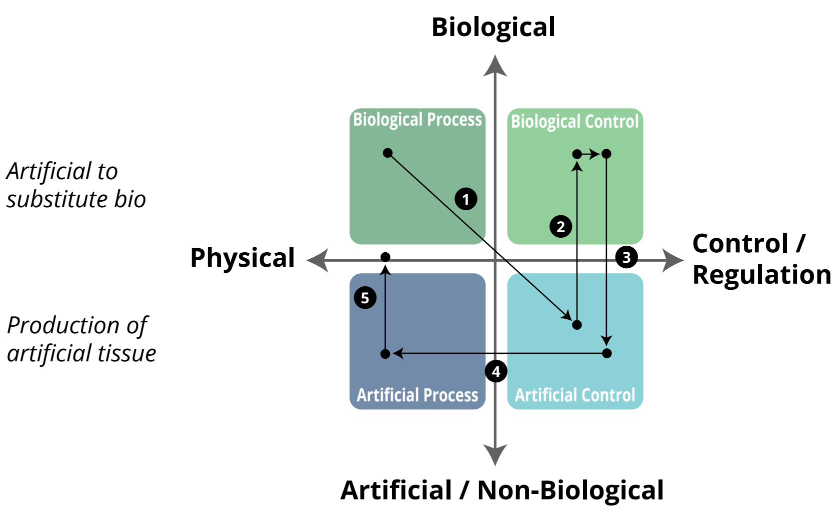


Figure 7.11 *Logic sequence in the field of action of Biointelligent Manufacturing for the process Tissue synthesis, as an example of the paradigm Artificial to substitute bio: 1. biotissue digitalization; 2. reverse engineer; 3. product/process design; 4. process implementation; 5. synthetic tissue*

7.3. From Strategy to Business Models

The business model describes the logic by which an organisation creates, distributes, and collects value. In other words, it is the set of organisational and strategic solutions through which an enterprise acquires competitive advantage.

In particular, the business model:

- provides guidelines by which the company converts innovation into value acquisition (such as profit for profit organizations, or community goals for a public administration or an NGO) without compromising of an adequate strategy capable of bringing a competitive advantage over the competition (thus draws a direction to which followers will probably follow);
- defines an organisation that allows to share knowledge within the company and enhances its human resources favouring the ideal conditions to encourage innovation;
- identifies relationships of interaction and cooperation with suppliers and customers (market) enhancing their choices (model and/or business);
- establishes the methodologies and tools to analyse critically and continuously the results obtained by its business model, comparing them with those of its competitors.

The structure of the business models is reported in Figure 7.12, where it is clear that different aspects need to coexist to improve a new business and increase competition among enterprises and, more in general, among business markets.

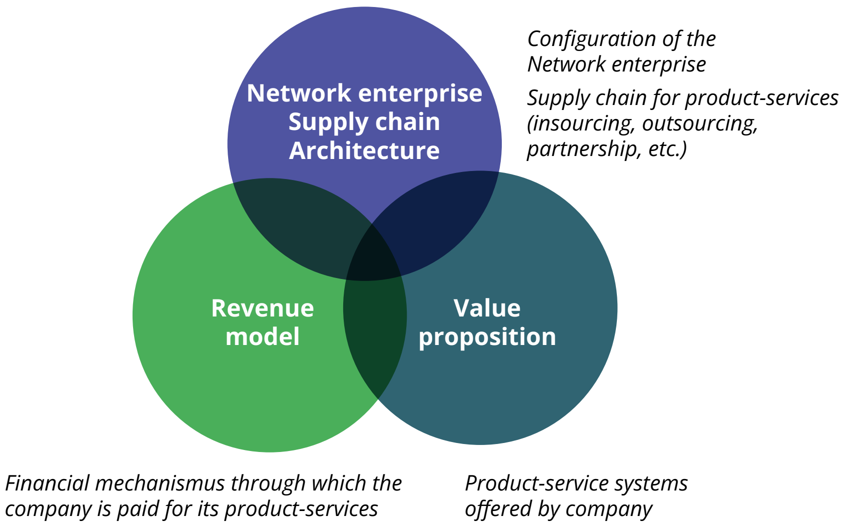


Figure 7.12 *The general scheme of the Business Models*

In the specific case of Biointelligent Manufacturing, the coexistence of bio materials/products with the non-bio, artificial world significantly intervenes in the business models. This requires a major of existing models which need a careful contextualisation in the production cycle as they require a new concept of cycles and production processes to preserve the characteristics of the bio material/product.

One of the most outstanding points is related to managing the biological contributions because it is necessary to consider:

- perishability of living material
- safety of people and environment
- safety of equipment
- post process with organic material normally not alive

The supply chain is the process that allows for creating a product or service and bring it on the market.

It is therefore a complex process that involves multiple professionals, activating numerous processes of the ecosystem-enterprise: from the supply of raw materials, the transformation processes, up to the distribution logistics that provides to bring the goods or the services to the customer.

Supply chain links are the individual steps that make up the supply chain. It is possible to identify four main phases:

- transformation
- storage
- defence
- logistics

7.4. Supply Chain: Transformations in Biointelligent Manufacturing

One of the main questions that arise is: What makes Biointelligent Manufacturing different from classical manufacturing?

In this section, through the analysis of the transformation phase, based on the logic sequence reported in Figure 4.1 of clause 4.1, an attempt to answer this question has been given through the identification of some possible production configurations that will characterise the production processes and systems in the near future.

1. **Production system to manufacture biointelligent products**

   Biointelligent products are manufactured by biointelligent systems. A biointelligent product results from the combination of biological and non-biological components. Biointelligent Manufacturing needs to manipulate both bio and non-bio materials and combine them to create those products.

EXAMPLE 1 (Figure 7.13): To produce a biosensor, there is a need of a certain number of cells. These cells must be in the correct quantity and correct state (e.g., alive). Therefore, in a manufacturing system, it is necessary to manipulate biological material (amplification of cell DNA, duplication of cells) and perform quality checks (cell counting, verify their characteristics, etc.) at the same time with operations and checks on artificial parts. This introduces considerable complexity. Different types of Biointelligent Manufacturing transformations may be present in a Biointelligent Manufacturing system. In the following, the archetypes of these transformations are defined.

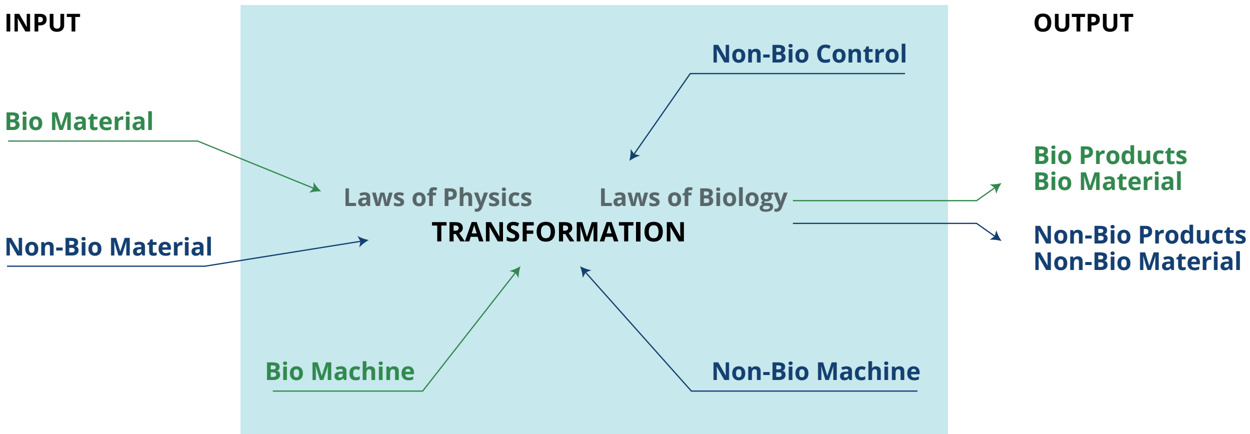


Figure 7.13 *Example 1: Production systems to make biointelligent products – the case of biosensors production*

2. **Production system integrating bio and non-bio components**

   Machines and systems integrate bio and non-bio components to create products.

   EXAMPLE 2 (Figure 7.14): Systems producing food can integrate biosensors that allow evaluating the quality of the final product (food, which is organic but artificially produced and can be monitored with biosensors which could be more effective than artificial sensors, for example, in detecting mold).

   EXAMPLE 3: Measures for risk prevention, safety at work and environmental risk control may be based on biological entities, which would result in the use of biosensors, for example for air quality monitoring. For instance, biosensors can measure the concentration of metallic dust in the air during metal powder additive manufacturing. If thresholds are exceeded, the system evacuates the employees and aerates the working area until the concentration is reduced.

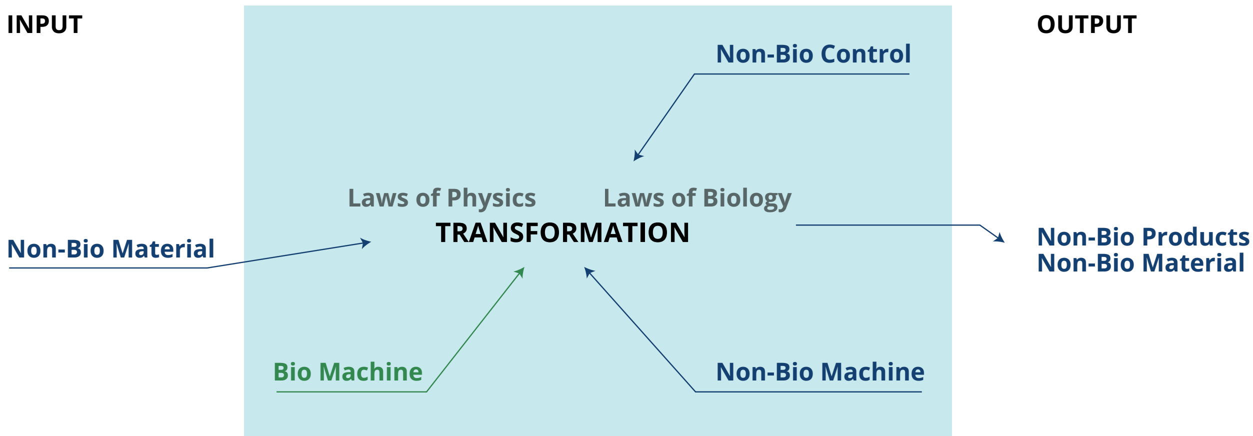


Figure 7.14 *Example 2: Production system integrating bio and non-bio components – The case of biosensors used for air quality monitoring*

3. **Intelligent non-bio systems that guide cells to perform pre-ordered tasks**
   The intelligent non-bio machine and system use cells as biological transformation cores to obtain the desired product.

   EXAMPLE 4 (Figure 7.15): A bioreactor that is a non-bio device creates the conditions for the cells to operate in the desired manner.

   EXAMPLE 5: Mechanical stress can be applied to induce cellular differentiation or change in cellular phenotype, e.g. in muscle precursor cells.

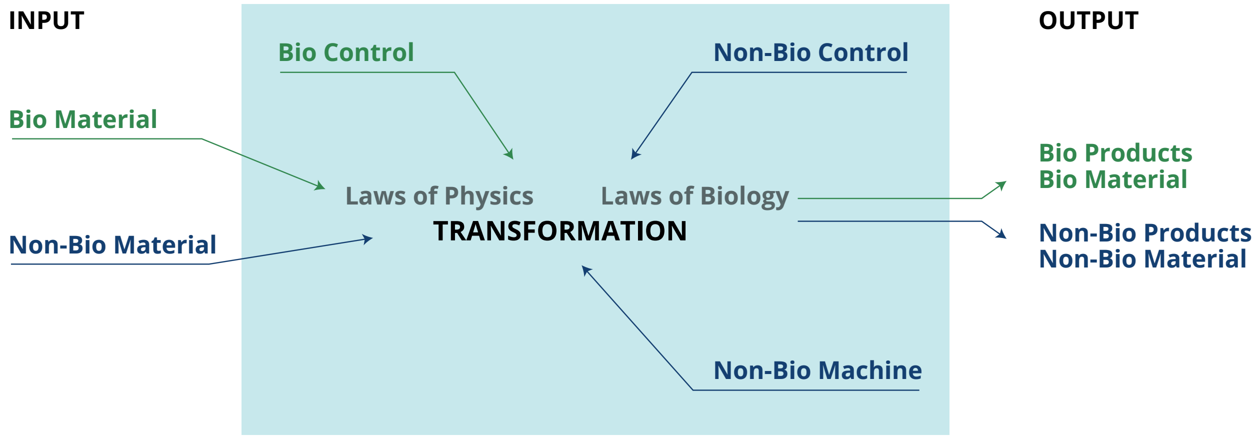


Figure 7.15 *Example 4: Intelligent non-bio systems that guide cells to perform preordered tasks – The case of a bioreactor*

7.4.1. Supply Chain Architecture: Storage and Defence Machine in Biointelligent Manufacturing and Correlation with Network Enterprise and Logistics

In addition to transformations intended to convert materials into products, a Biointelligent Manufacturing system integrates also other transformations. For example, a warehouse is a machine that defends the product during time. The defence in this case is simple, i.e., the product is left on a shelve, wrapped, secured and locked in a hall and nothing happens over time until the product is needed and shipped. In the "bio" case, the defence is normally much more complicated. The refrigerator, for example, is basically a warehouse designed to prevent unwanted transformations of the product which would entail its degradation. Therefore, it shields the product/material from external agents and/or forces that intend to enter to destroy it. It is necessary to reconsider the concept of "defensive machine", considering that it needs to act against external physical agents (the temperature, the presence of dust, etc.) and active external agents (bacteria, mold, etc.), so the defence machine should have both physical and biological skills. The need of defensive machines is due to the need of performing time transformation, because it is not always possible to use bio product/material immediately after it has been obtained. Therefore it has to be kept alive or organically preserved for the moment it can be used in subsequent transformations in the production cycle.

In the production system, it is frequently possible to control transformations very well. But when a transformation is completed, the product enters the world where the forces are enemies and where defence is complex and therefore it could be very expensive. Therefore, strategical decisions have to be taken, as whether it is convenient to concentrate the production in one location to minimise the transfer of material and to make costs affordable (a clean room for chips production is a good example: the defence machine is the clean room that is energy-intensive and expensive and can only be centralised).

A defence machine,[25] more or less expensive, will push to divide or integrate the activities in the supply chain: if it is inexpensive, then it is possible to think to perform the transformation steps in different locations; if, on the contrary, it is expensive, transformations need to be concentrated in the same place. These aspects influence the structure of the Network Enterprise for Biointelligent Manufacturing: Network Enterprise becomes impossible when the cost of defence is too high. And this is where the supply chain architecture is outlined, that is, the strategy depends on the defence machine sometimes even more than on the transformation machine/system.

Therefore, the defence machine is an important part and defines the extension of the Network Enterprise, making a parallelism with the importance of the cool chain for human evolution. It is possible to understand how important it is probably for Biointelligent Manufacturing to develop adequate defence

25 JOVANE, Francesco; CARLESI, Luca. The Elementary Machine: an 'Atomic'Model to Analyse and Devise Production Systems. CIRP annals, 1989, 38.1: 179-182.

machines. A clear example of how complex and expensive it can be to build an adequate defence machine, is the Covid vaccines and the difficulty of their logistics and storage at -80°C. Considering the refrigerator as a defence machine for the biological sector in general, this machine defends only from a physical action of temperature. A more complex biological defence machine is in place in laboratories dealing with microbes or viruses which include expensive and complex filtration systems as well as containment devices.

In Fig. 7.16 is represented an ideal concept of defence machine in the field of Biointelligent Manufacturing. The defence machine (light blue circle) can be considered a machine able to preserve what is inside, but it should be able also to protect what is outside from what is produced inside and that is able to manage both bio and non-bio materials/products.

It is necessary to think that the defence can be actuated at different steps, so for example (Figure 7.16) It can be created a system in which both a non-bio machine/system (green circle) and bio machine/system (violet circle) can coexist. Both these machines/systems have a controlled door through which material or products may enter or leave so that a transformation can take place.[26]

The outermost system (light blue circle) may be necessary a controlled environment with respect to external forces and agents is needed. This approach would allow to minimise the development of the defence systems of bio and non-bio internal machines and therefore to have a more controlled environment both with sensors and with additional machines/systems that perform themselves an action on the bio and non-bio machines/systems.

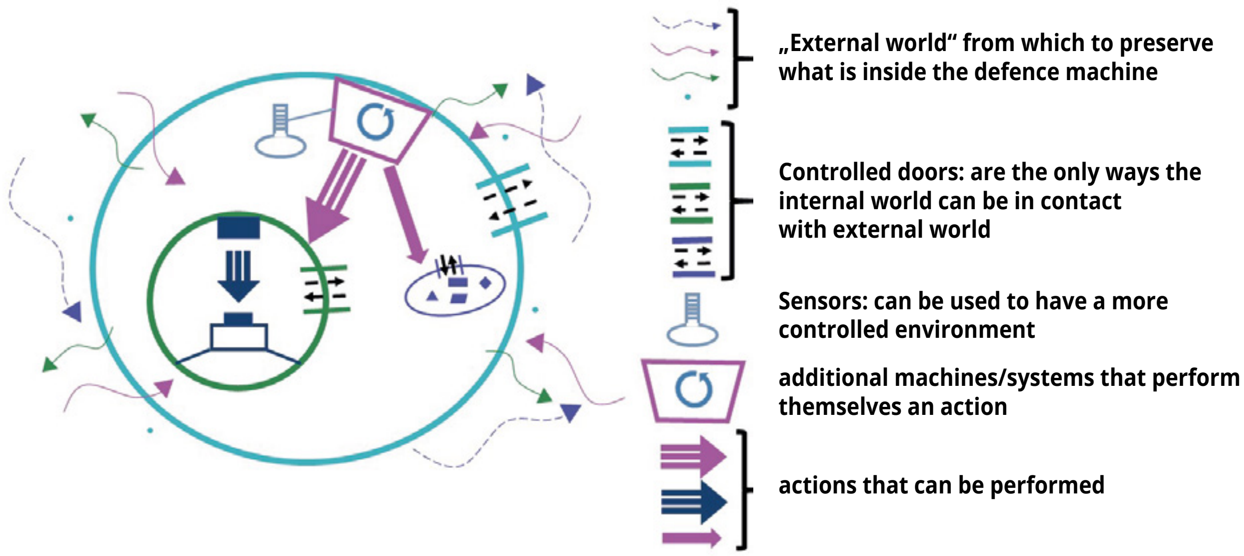


Figure 7.16 *An ideal scheme of a Biointelligent Manufacturing Defence machine*

26 Consider that in some systems the bio and the non-bio machines can be the object of the transformation. In other words, in some particular cases, the machine may transform itself

7.4.2. Value Proposition and Revenue Models

The value proposition can be defined as the set of benefits that an enterprise promises the customers and from which they can derive satisfaction (customer satisfaction). This can be, for instance, to justify the payment of the relative cost. It consists of a brief description of the characteristics and product's/service's attributes with respect to the needs and expectations of the potential buyer. It tends to focus on the elements of uniqueness of the product/service compared to the competition to make it attractive in the eyes of the consumer.

A well-constructed value proposition must, in fact, provide compelling arguments as to why the consumer should buy just this product. It is a matter of highlighting unique strengths over competitors, which can provide a real competitive advantage that, for example, can result in higher-quality products, faster market response, lower costs, or higher innovation.

In the case of Biointelligent Manufacturing, a standard value proposition is not expected because the offer is not only related to a product/service. With biointelligent products, the interaction with humans will be different and more pervasive than what happens for example for a drug that performs a specific function. What has been hypothesised in the previous paragraphs is a more complete interface, where biological and artificial interact by possibly having biological components in the product. Two different levels of value proposition are expected:

- first level: generate new artificial products using also bio processes. The value proposition is important because it will be possible to produce products that could not have been done before the biointelligent transformation
- second level: two types of products, those that interact with the bio part but that have nothing bio (drug) and those that are also bio and therefore interact with the bio part in a different way than before (vaccine)

The value proposition's potential is immense because it can produce both products and services that could change the world. It is expected to receive usable value proposition in the medium term. They are linked to new products that use the biological component or new products that could not be made without Biointelligent Manufacturing.

A revenue model is a framework for generating financial income. It identifies which revenue source to pursue, what value to offer, how to price the value, and who pays for it.[27] It is a key component of a company's business model. It primarily identifies what product or service will be created to generate revenues and how the product or service will be sold.

Without a clear and well-defined revenue model, a plan of how to generate revenues, new businesses will more likely struggle due to costs that they will not be able to sustain. By having a revenue model, a business can focus on a target audience, fund development plans for a product or service, establish marketing plans, begin a line of credit, and raise capital.

It will probably be possible to start from the classic models for Biointelligent Manufacturing because, as introduced above, they are based on financial aspects. The lack of appropriate revenue models can stop the transition toward Biointelligent Manufacturing. Especially in the first stage, it is expected that a market alone will not be able to support the evolution. Therefore, focused support from the public is needed. This may involve support to the research at different TRL levels as well as support for establishing connections among actors not used to working together and pilot plants to demonstrate the viability of new approaches. In this phase, an investment will be too risky even for venture capital. Therefore, a robust and targeted public intervention is needed. The speed of public intervention in this field is of paramount importance since actors moving in the first stage may easily acquire a dominant position in the market related to the cumulated volumes produced. This is very difficult to change at a later stage. Therefore, if Europe wants to be in the driving seat of Biointelligent Manufacturing, European and National funding bodies should act quickly and powerfully.

27 Wagner, E. 2013. 5 Business Model Components Every Entrepreneur Needs [online]. Available from: https://www.forbes.com/sites/ericwagner/2013/05/23/5-key-business-model-components/[Accessed 20 October

8. Skills and Education

8.1. Introduction

It is important to invest in and to improve training and education to prepare future and current workers and the society for technological change in industry. These changes will be felt at all levels: science, technology, engineering and mathematics, computer literacy, language and art education. Better, forward-looking regulation, a more flexible business environment and a high-quality, technology-based education policy would enable greater freedom to innovate and accelerate the transformation of the European economy, creating a more entrepreneurial, innovative, fair, and resilient society. The remaining fragmentation between education, science, technology, and innovation policies should disappear with a view to achieving greater synergies and joint action. In addition, it would facilitate the development and use of advanced technologies in the training of qualified professionals in a coordinated manner.

Education and lifelong learning must be seen as critical factors for adapting to new, rapidly changing technologies and working methods for workers at different levels and in different roles. Thanks to technology in production, new career opportunities are emerging for talented people who meet a new job profile. Innovation is taking place and developing at an unprecedented pace, driven by knowledge and innovation communities, clusters, collaboration between research organisations and industry. New and faster methods and channels for innovation advice, support, and technology demonstration, such as digital innovation hubs, lubricate this innovation pace. Public education, education and retraining systems, the media and business associations play a very important role.

The increasingly growing integration of advanced technologies, new manufacturing methods such as Biointelligent Manufacturing, and the resulting changes in manufacturing process management practices have created a need for new skills. In manufacturing companies, this means that the nature of operators' work has changed from labour-intensive to less manual but more technology-intensive. This requires more qualified staff, who needs to keep up to date with the technological changes in the equipment, materials and production processes. Ancillary services, logistics, management, and engineering are also evolving and use more technology to create ever-expanding technological support for manufacturing operations. As a result, the employment of low-skilled workers is declining rapidly, while skills gaps and disparities expand. Also the pay gap between skilled and unskilled workers is getting wider. On the other hand, new directions of production, new career opportunities, for talented people with a new job profile are emerging.

Obviously, this will have a direct impact on the change in vocational education and higher education systems, which is already too slow and unable to keep pace with technological change. As the pace of combining physical, digital, and bio-technologies will increase, this will put even more pressure on education systems. For education policy makers, this means even greater rates of transformation.

The good news is that the same technologies can accelerate change in education, but new teaching methods, such as teaching factories, training factories, hybrid laboratories, and more, are needed to implement them in educational institutions. Technological developments force educational institutions to frequently update vocational training and study programs and create new curricula that are available not only in initial training but also for workers in companies at all levels who want to upskill or reskill and to keep pace with technological evolution. To meet this challenge, education policy-makers need to encourage educational institutions to establish and maintain regular contact with technology manufacturers in order to maximise the circulation of curricula, teaching materials, and lecturers' knowledge through direct access to curriculum directly from technology developers and manufacturers.

Collaborative infrastructures, such as „sectoral centres for practical training“ and changing education and training paradigms, such as „Training Factories“ or „Hybrid Laboratories“, have the potential to engage in this type of collaboration with industry (usually large companies or associations representing SMEs).

Due to the need to train employees and students on Biointelligent Manufacturing, the method of hybrid learning that includes online training, peer-teaching, and a mastery learning methodology in learning or teaching factories will be much more efficient than conventional learning techniques currently practiced in teaching skills.

8.2. Fields of Action

Hybrid learning in teaching or learning factories incorporates several different learning modalities to achieve learning objectives in a single course. In this proposal, online education modules serve as an introduction to skills and knowledge that are then combined with a live teaching and learning methodology that includes peer-teaching amongst students using a checklist system that evolves with complexity while building mastery in the skills being taught through practice with feedback.

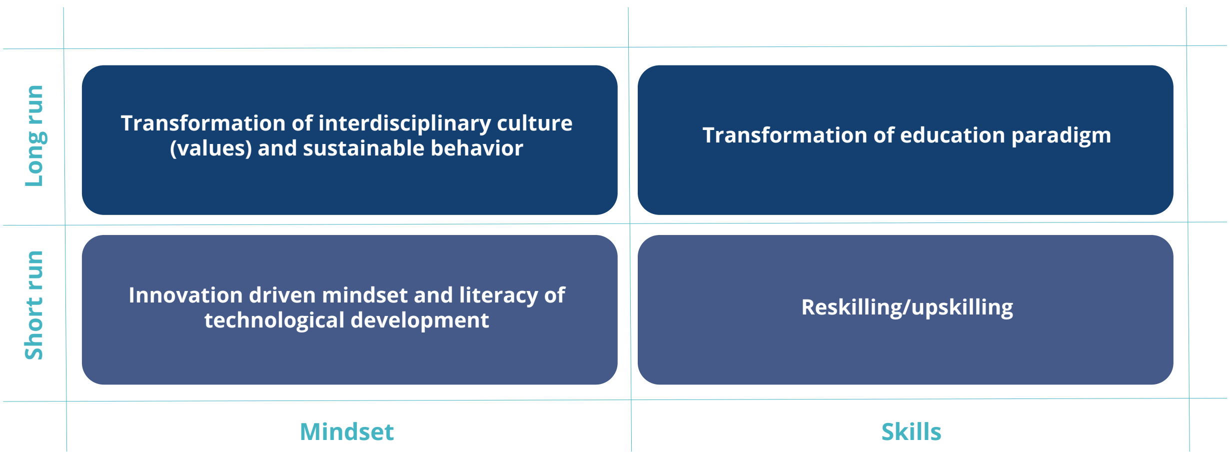


Fig. 8.1 *Interdisciplinary collaboration and education with natural scientists will be a key prerequesite to develop future proof manufacturing skills*

8.3. Development of Methods for Interdisciplinary Teamwork

Managing climate change is a major challenge for the world. As mentioned before, today, one of the most explored and promising concepts is learning sustainability from nature. The observation of the natural world has steered humanity's efforts to evolve products and production processes, by replicating the processes and their outcome in the biological environment. There is a growing belief that such technological evolution, repeating naturally occurring physical and biological processes in the products, will help to regain the same capacity as the natural world to innovate in new and more advanced forms. The manufacturing industry increasingly engages in a new green circular economy deal. From this paradigm of circularity the industry of the future will start – from the basic concept that what is produced must be used to redesign new products in a new production cycle. And, that this must be repeated as often as possible. Because the technologies to achieve this will be increasingly advanced and complex, more and more collaboration between disciplines is necessary to decipher and address the technical and scientific issues that will arise during this journey.

Being interdisciplinary by definition, the Biointelligent Manufacturing paradigm relies on the successful interdisciplinary teamwork, spanning through various levels – from lab product developments to inter-industrial symbiosis. Due to the uniqueness of processes, the demand and formation of necessary skills has to be designed at early stages of production planning. On a positive note, the majority of Biointelligent Manufacturing processes originate from scientific and engineering teams, who are able to organise themselves and have a good background in creating ad-hoc interdisciplinary teams. This good practice is paramount in both educating new professionals who must be involved in research projects during their higher education, and in understanding the value and principles of cooperation. At the same time, these young professionals should be systematically trained to carry the skill of identifying the need of interdisciplinarity and be able to join or form teams necessary for solving complex tasks. While this is often emphasised in many engineering and life science curriculums, in reality, the graduates often have much stronger vertical bar of the "T" and struggle when communicating their knowledge to interdisciplinary teams. The principles of leadership and management, team climate, transparency, communication, respect, allocation of resources, and other well-known methods need to be continuously communicated.

8.4. Collaboration of Life Sciences, Engineering and Information Technology

The observation of nature and the perception of its complexity have also led to efforts recreating it in the digital and physical world. As it is described in the R&D clause 6, scientists are now trying to make physical and digital systems intelligent and evolve them sustainably. This is a complex task that requires networks between professionals in different fields.

The transition from the digitalisation era and the 4th industrial revolution (Industry 4.0) towards the new paradigm of biointelligent systems implies interdisciplinary work. Main actors of this industrial transformation are in medicine/life sciences, engineering/automation, digital tech/big data. Each of the specialists in these areas will be able to support this transformation. By investing in the national education systems of the member states and by upskilling and reskilling employees of the specific sectors we contribute to a new scientific, economic, ecologic, and skills era of Biointelligent Manufacturing.

Imprint

DOI

DOI: 10.24406/publica-607

Publisher and Copyright

Manu*FUTURE* sub-platform Biointelligent Manufacturing (BIM)

Website: www.biointelligentmanufacturing.org
E-Mail: secretary.bim@ipa.fraunhofer.de

Authors

The members of the Manu*FUTURE* sub-platform Biointelligent Manufacturing (see below)

Key editors

Eric Maiser (Chairman), Jessica Horbelt, Martin Thoma, Yannick Baumgarten,
Bianca Maria Colosimo, Merja Penttilä, Tullio Tolio, Gianluca Trotta, Günter Hörcher, Gintaras Vilda

Editing and typesetting

komwerb Agentur, Eberdingen, Germany

Fraunhofer Institute for Manufacturing Engineering and Automation IPA
Nobelstrasse 12, 70569 Stuttgart, Germany

Biointelligent Manufacturing is a sub-platform of MANU*FUTURE*-EU