NSF/ASME Student Design Essay Competition
Challenges in the Design of Complex Systems

# "BioX Technologies, a 2035 Global Sustainable Enterprise"

Nafiseh Masoudi and Jebin Biju

Clemson University, Clemson, SC

**(Graduate Category)**

## Abstract

In today's era of technology advancement, transplants are becoming obsolete. Now regenerative medicine and tissue engineering have successfully researched the possibility of producing artificial organs using humans' actual cells. This will help expedite the process of treating patients without the need to stay in long waitlists for an organ donor.

BioX is a manufacturing enterprise invested in producing artificial organs and implants. As a global manufacturing enterprise, BioX seeks advice from our consulting group in order to become a leading global enterprise by the year 2035. This report summarizes our advice to BioX's CEO.

## BioX: a Leading Global Manufacturing Enterprise

By the year 2035, industry 4.0 will not be in its infancy anymore and global manufacturing enterprises will work based on all the nine pillars of this model shown in Fig. 1. The implementation of these practices will result in decentralized manufacturing systems that increase the efficiency of the factories and lead to optimized production flows [1].


*Fig. 1 Elements of Industry 4.0 [20]*

The global manufacturing companies will create, store, process, and analyze big data. Big data includes large amounts of heterogeneous multi-source data. The collection, storage, and analysis of big data from various sources (from operation to customer management) support real-time decision making and enhance the company's competitiveness and productivity [1].

The cloud infrastructure will facilitate services such as storage and computing of the big data by delivering the services over a network without the need for purchasing any software or hardware [2]. In addition, the deployment of cloud computing will create a more collaborative and innovative environment within a global enterprise like BioX [3].

Another important element of industry 4.0 to be considered within the operation of BioX is cyber-physical systems the security of which is paramount. Cyber-physical systems are collaborating computational entities that are connected to the physical systems and have access to and process the big data of the system [4]. In addition, BioX will be a more connected manufacturing enterprise in the future and as a result, different departments within BioX as well as the supplier and customer will all be integrated horizontally and vertically as a more cohesive unit [1].

Robots have long been used in manufacturing. However, the emergence of industry 4.0 makes even greater use of their autonomy and flexibility to work alongside humans and other autonomous systems safely and efficiently and even learn from them [1]. Therefore, BioX will also benefit from this new level of autonomy for example in bioprinting organs with robots and delivering packages using autonomous electric vehicles. Simultaneously, BioX will take advantage of augmented reality which provides real-time information that could assist the workers in decision making and work procedures[1].

Additive manufacturing technologies have been used in a variety of industries for decades due to their superior properties over the traditional subtractive manufacturing. However, there are still some challenges in the additive manufacturing of high-quality products that BioX will need to overcome in order to become more competitive. This is further explained in the next section.

Furthermore, real-time simulations will be heavily used in BioX to reflect the physical behavior of machines and processes and aid the operators to for example select an optimized setting for a more productive operation of a machine [1]. Lastly, the integration of the industrial Internet of Things (IoT) will enable more devices to communicate with each other which can assist the field workers and devices to make real-time decisions [1].

Even though the evolution of industry 4.0 practices provides the necessary infrastructure for enterprises to achieve productivity and stay competitive, the sole dependence on these practices may not be sufficient to become a leading global enterprise in 2035. Instead, researchers have proposed some practices that separate a world-class manufacturing organization from traditional organizations. Some of these practices include total quality management, employee involvement, lean manufacturing, customer relationship, total productive maintenance, and leadership [5]. All these practices could be summarized in one word, *sustainability*.

As noted in [5], US Department of Commerce defines sustainable manufacturing as “using processes that minimize the negative environmental effects, conserve energy and natural resources, are safe for employees, communities, and consumers, and are economically sound to manufacture products.” Therefore, sustainability has three implications: environmental, social, and economical.

To achieve sustainability within the BioX company our consulting group recommend using a framework suggested by Dubey et al. [5], which encompasses all aspects of manufacturing and includes lean and green practices to minimize waste and stay environmentally responsible. The details of this framework are presented in the “Sustainability and Green Manufacturing” section.

In addition to sustainability, a leading global enterprise requires access to high-end technologies to design and manufacture high-quality products. Some of the technologies BioX is incorporated to reach and retain its global leading image are discussed in the next section. To sum up we deem three characteristics in a global leading enterprise:

- Integration of industry 4.0 practices
- Access to and integration of world-class and competitive manufacturing technologies
- Sustainability through lean/green integration in order to reduce waste

## The Technology of Bioprinting Implants

The emergence of additive manufacturing (AM) technologies has revolutionalized many industries with its substantial advantages over traditional manufacturing including fabrication of complex parts, design freedom, waste reduction, and fast prototyping [6]. BioX Technologies is founded based on this advanced manufacturing technology and utilizes bioprinting methods to produce artificial organs and implants.

The bioprinting technique employed in this company relies on five major components, (a) a blueprint of the organ, (b) a bioprinter, (c) a cartridge that holds living cells, (d) hydrogel or scaffold, and (e) bioink [7]. One of the main challenges in realizing organ bioprinting is the integration of these components to support automation and mass production. The problem is not solely to design and manufacture; the designers need to address biomedical, thermal, and fluid aspects. Hence, a closer look at the bioprinting components helps identify potential challenges.

### Blueprint

The additive manufacturing process requires a digital blueprint of the part that needs to be printed. Generally, additive manufacturing uses a single material; hence, only the geometric features of the part are of importance. However, more information needs to be fed to a bioprinter since organs contain different cell types with different densities at various locations. In addition, organs may have areas that are highly porous; hence, the STL file requires large memory to be stored and heavy computation to design and manipulate [8].

Medical scanning methods as Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) scans can give detailed images of the organs. Therefore, instead of STL, bioprinters in BioX can take image inputs in the form of MRI or CT scans from multiple angles of an organ to capture all the details. These images are then converted to a voxel-based solid model using an embedded software to incorporate tissue adhesion, retraction and compaction [9]. Thus, the final blueprint is generated by clinical imaging of the patient-specific organs. Using the clinical images of an organ, not only requires less storage and computation for complex shapes, but it also eliminates the accuracy issues of STL that occur due to approximating curved surfaces.

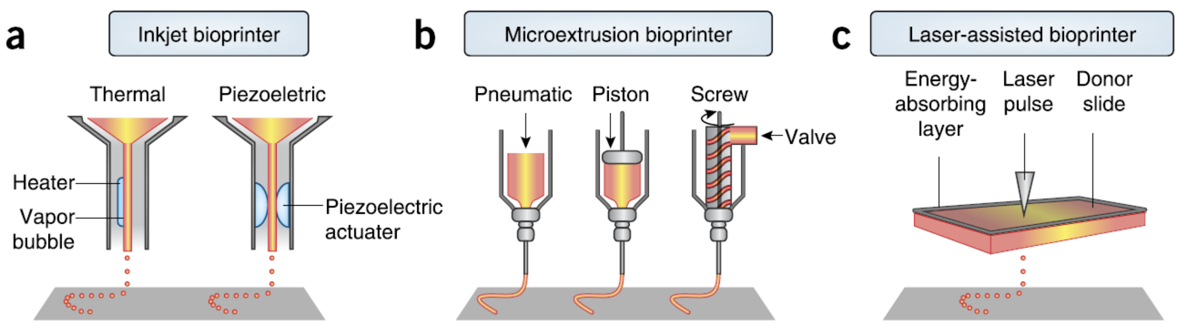



*Fig. 2 Components of Inkjet, extrusion and laser-based bioprinters* [10]

## Bioprinter

The most commonly used bioprinters are inkjet-based, extrusion-based, and laser-based. These bioprinters deposit biomaterial (ink) through orifices using either thermal, piezoelectric excitation in the case of inkjet, mechanical piston or screw-based devices in extrusion printers through an orifice and finally, laser beams in the case of Laser-based printers [10,11]. Fig. 1 illustrates these processes.

As discussed earlier, organs cannot be visualized as a homogenous single-material part, which makes these techniques difficult in practice. Instead, BioX takes inspiration from these techniques and develops an automated system capable of printing functionally graded parts.


*Fig. 3 Components of the BioAsemblyBot® [12]*

Since different cell types with different properties need to be printed, robotic arms could accurately deposit biomaterials spatially and bring about a level of automation to the process. BioAssemblyBot® is an extrusion-based robotic bioprinter used in BioX (Fig. 3). It has a 6-axis robotic arm that is capable of printing multiple materials. It can also scan 3D objects and print on them as shown in Fig. 4 where it is printing a pattern on a heart's model [12,13]. BioX uses these hydrogel printing bots that work based on layer-less 3D printing.

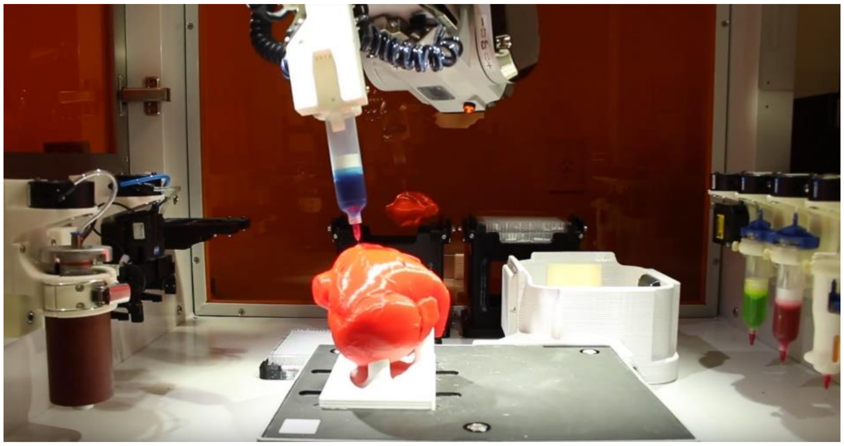


*Fig. 4 BioAsemblyBot® printing on a Heart model [12]*

This method eliminates the staircase pattern caused by layer-by-layer printing and therefore, removes the need for post-print finishing processes to achieve the desired surface precision. Layer-less manufacturing also does not require slicing of the part a priori and results in more isotropic parts which do not compromise the mechanical properties of the part compared to layer-by-layer manufacturing. Furthermore, the multi-axis head of the bot enables printing on different build planes and orientations of the part, hence, removing the need for support materials which reduces the material waste.

### Bioreactor

Bioreactors are chambers that recreate the necessary environment for the printed organ to stay viable and at the same time allow them to assemble, compact, and remodel into functional tissues [14]. In tissue engineering, after the tissue is made, it is put into the bioreactor to mature. However, for 3D thick tissues, due to the nature of the bioink and the high resolution of the printing, organs will take hours to be printed, making the cells inviable by the time the part is transferred to the bioreactor. To combat this issue the organ printing setup in BioX is placed within a bioreactor that provides the conditions for the tissues to stay viable during the printing process.

### Cell viability and vascularization

Biomaterial on its own does not take a certain shape. Hence, biodegradable scaffolds are 3D printed to act as an initial framework for the tissue. The bioprinter deposits hydrogel, containing cells, onto these scaffolds, which on maturation and tissue assembly holds the shape of the construct even after the scaffold material is degraded. Nonetheless, the main challenge is the vascularization of the tissues and keeping the cells viable post printing, or keeping the organ alive. To keep the organ functioning it needs to get the required nutrients and oxygen, which is difficult to accomplish because this role is played by the blood cells and the complicated vascular system within the body. Thus, printing the organ alone is not enough. Research has been

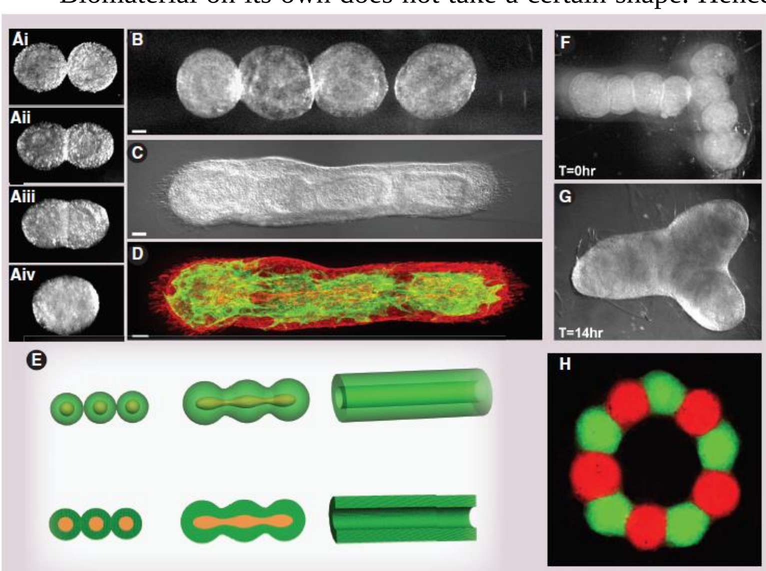
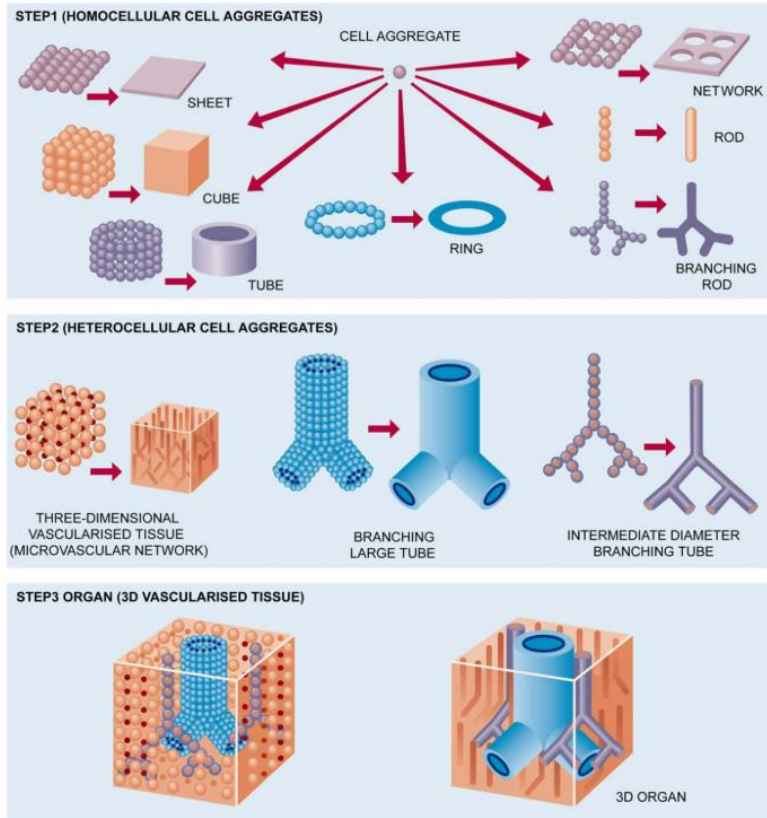



*Fig. 5 Self-assembly of tissue spheroids [7]*

carried out to create an artificial vascular system in the organ that would mature into a natural construct that would be integrated into the human body [11]. BioX deploys the latest development in vascularization: printing vascular networks using cell aggregates [15].

To resolve the low accuracy of cell placement on the scaffolding and complication in multicellular placement scaffold-less printing has been researched and the focus has shifted from using hydrogels, which are unable to maintain shape, to cell aggregates [7,15]. Cell aggregates are a group of cells which are usually in a spheroid shape (see Fig. 5).

This provides the opportunity to directly bioprint 3D tissues without scaffolds. The process is demonstrated in Fig. 6 and is currently practiced in BioX. It also eliminates the issue of generation of harmful byproducts from the degradation of the scaffolds. Additionally, as cell aggregates enable the embedding of vascular networks that keep the cells viable, BioX is now capable of in-situ bioprinting where the organs could be printed directly into the human body [15,16], for example for reconstructive surgery after the removal of a tumor (Fig. 7).



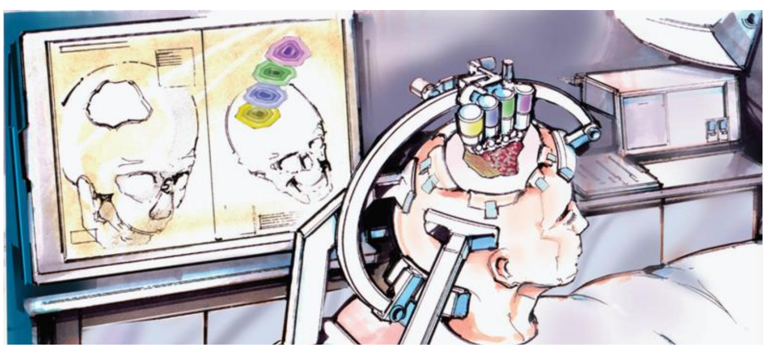



*Fig. 7 Concept of in situ bioprinting [17]*

## Bioink

Bioink is the base material used in printing tissues and organs and is essentially cells immersed in a hydrogel. Bioink is sensitive to shear stresses when it comes out through the nozzle [11]. Thus, it is preferable for it to have low viscosity. However, to print larger organs, high viscous bioink is required, because low viscous ink does not retain its shape after printing. This conflicting viscosity requirement is a challenge which could be further researched in collaboration with academia.

## Overall Design Process

A summary of the overall design and manufacturing process of the artificial organs practiced in BioX is shown in Fig. 8. As shown in this diagram, the design process starts with the analysis of customized requirements.

Next, the CT-scan and/or MRI data is used to create a CAD model of the part. This data is then inputted to FEA and optimization analysis software so that a final optimized model can be generated and inputted to the bioprinter. Before the bioprinting starts, the optimal path of the robot’s arm is also found. After the bioprinting is completed, non-destructive tests such as ultrasonic imaging are used to assure the quality of the part and find potential defects within the part to be fixed or reprinted.

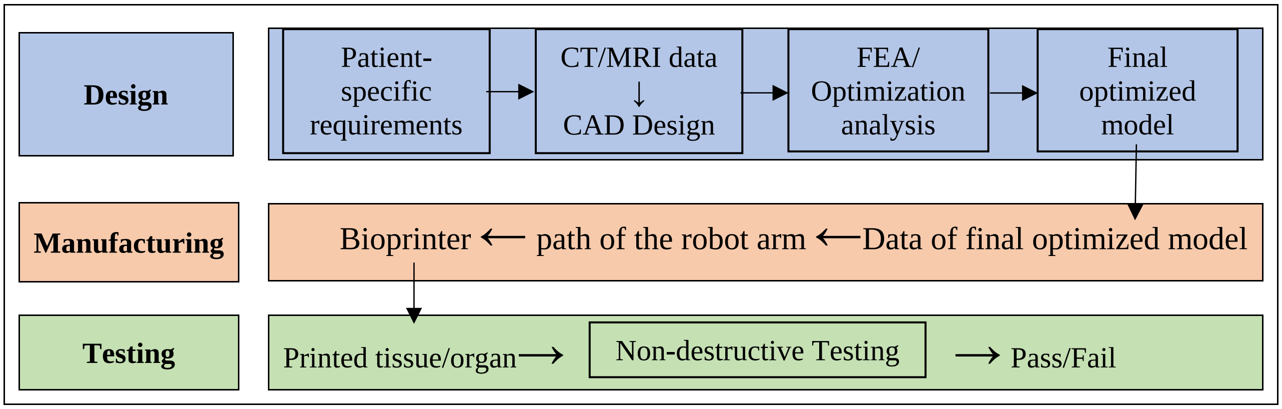



*Fig. 8 Process of design and manufacturing organs at BioX* [17]

## Sustainability and Green Operation

As discussed earlier, sustainability is a criterion to become a leading global manufacturing enterprise. Based on the model developed by Dubey et al.[5], there are eight different identifiers that characterize a world-class sustainable manufacturing organization as shown in the diagram of Fig.9. These factors can address the social, environmental, and economic aspects of sustainability through the practices discussed as follows.

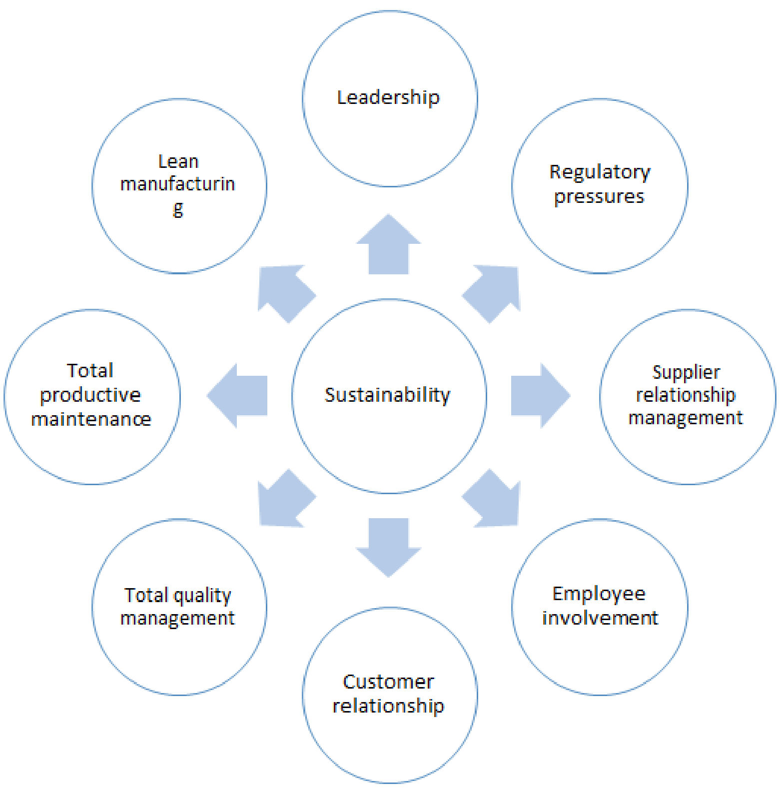



*Fig. 9 Characteristics of a world class sustainable manufacturing enterprise*

Among all these factors, lean manufacturing plays an indispensable role by focusing on eliminating eight sources of waste: overproduction, human resources (not using people's minds and have them involved), transportation (of tools and materials to the point of use), inventory, motion (movement of people), defects (rework or fixing products), overprocessing, and waiting (delays for materials, information or people) [18]. Lean practices can affect other areas within a company such as operation and leadership to enhance productivity by minimizing different sources of waste. In addition, as defined by Handfield et al. [19], green manufacturing is an economically-driven approach to eliminate all waste streams corresponding to the design, manufacturing, and disposal of products. As in the future the challenges of depletion of natural resources and waste disposal will become more serious, it is paramount for a leading global enterprise to take a direction in green practices.

Studies show lean and green are intertwined [20] and can be considered complementary[21], though the types of wastes associated with each are different. Green deals with the wastes that negatively affect the environment such as disposing of toxic materials, hazardous chemicals, and energy consumption.

Additionally, research shows green manufacturing practices decrease manufacturing cost, positively affect the company image, improve innovation, reduce environmental and occupational safety expenses, attract new customers, and in some cases improve product quality [22,23]. Therefore, to achieve the positive effects of lean and sustainable manufacturing, we recommend that BioX incorporates green manufacturing practices.

In this effect, a systematic green design and planning approach is developed by Deif [24] which could be implemented to improve and maintain the level of greenness in BioX. The goal will be to create products with less energy and resource consumption, substitute input materials (non-renewable with renewable and toxic with non-toxic), reduce the unwanted outputs, and convert outputs to inputs (recycling) [24].

The first step in Deif's process is the green evaluation which determines the state of greenness within the company based on these metrics: waste level (material wasted/not recycled and energy consumed), eco level (the environmental impact/pollution), and company's green culture (green practices and awareness of employees). BioX can benefit from a variety of methods including surveys, questionnaires, and Green Stream Mapping (the green counterpart of Value Stream Mapping) to acquire the necessary input data for green evaluation.

The second step is the preparation of a plan to improve the company's greenness based on its greenness level. This planning should be addressed at all the operational, process, and system levels. The plan will be likely a result of solving an optimization problem the sample objectives of which are minimizing energy and material consumption as well as total production cost. Constraints of this problem can be meeting the market demand, the accepted level of product quality, and time. The outcome of this optimization problem can determine the optimal process parameters and energy and material level to reach a greener state.

After a plan is well laid out, it needs to be implemented in the system to evaluate its efficiency. As the final stage, the achieved green state of the system needs to be maintained to ensure its sustainability. For this purpose, activities such as green Kaizen can be used to ensure continuous improvement by developing more improvement plans based on the feedback. A schematic of this approach is shown in Fig. 10.

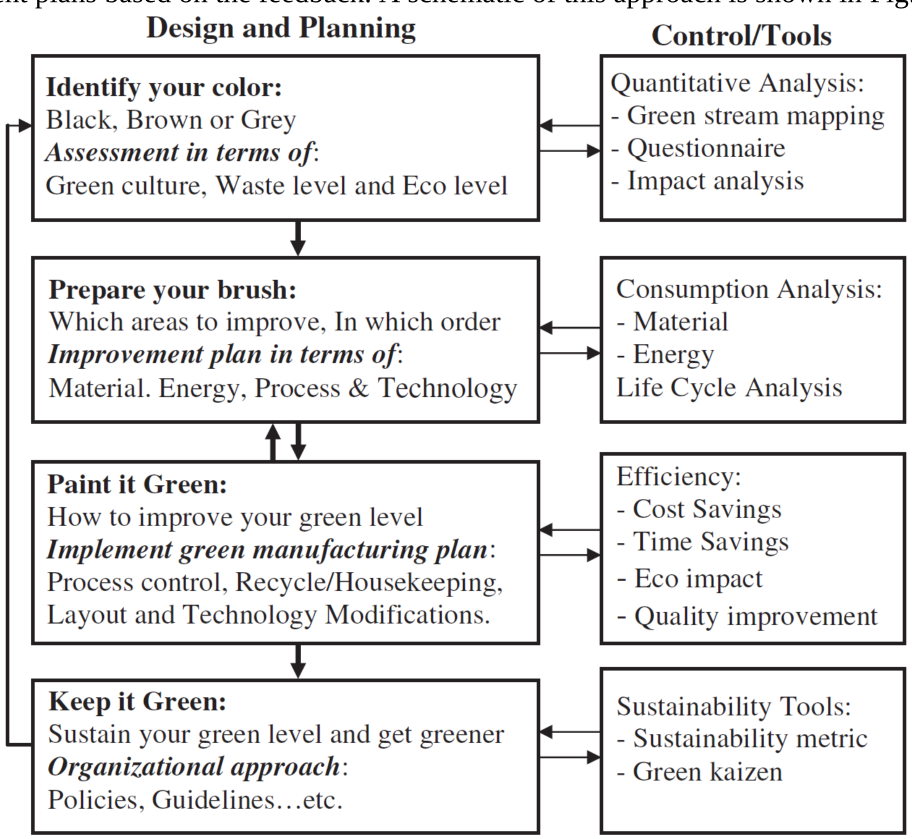



*Fig. 10 A systematic approach to green manufacturing* [24]

## Partnerships

The evolution of industry 4.0 and its descendants reduces the level of human involvement in basic tasks such as driving, delivering packages, operating machines, etc. However, this does not mean the present workforce will become unemployed in the near future. By the year 2035 robots will completely control over the mundane tasks such as assembling components in manufacturing lines and delivering packages which will transform human jobs from simple tasks with minimal required skills to skill-intensive jobs. Therefore, two higher education systems can be provided: two-year institutions that feed the technical needs of the manufacturing market by training skilled IT personnel and technicians who will supervise and maintain the autonomous devices and four-year institutions that focus more on the theoretical background of science and technology. BioX will benefit from both two-year and four-year students either through completing capstone design projects (only offered in four-year institutions) or working on more complex problems as interns and co-ops. Academic institutions and national labs will also collaborate with BioX on research projects to overcome the present challenges of the company and develop new methodologies to design and manufacture organs.

In addition to academic partners, BioX will need industry partners to provide the required infrastructures for its efficient and productive performance as a decentralized manufacturing enterprise. These industries will provide services for cloud computing, quality assurance, multi-axis manufacturing robots, delivering packages with autonomous electric vehicles, cybersecurity of the manufacturing systems, and virtual reality systems for process simulation. It is noteworthy that all these collaborations are based on the green practices discussed earlier and the employees will be regularly trained to maintain their awareness of the environmental considerations.

## Future Challenges and Research Directions

Due to the cyber-physical nature of the AM technologies, they are prone to security threats. For example, 3D printers may be connected to a network for remote submission and monitoring of jobs; simultaneously, trusted and untrusted parties may have access to the big data and be involved in the design process. The interconnectedness nature of novel manufacturing systems increases the possibility of attacks from outside sources [17] which may result in early failure of a job or bypass encryption. Although solutions are provided for temporary protection, they either have complications in practice or seem to work only in special cases [17]. In addition, as new solutions to cybersecurity problem are introduced, attackers will also adopt new ways to penetrate these systems. Therefore, a future research avenue can be to develop more permanent and real-time solutions to the cybersecurity of decentralized manufacturing systems.

Another challenge the BioX company will face is interoperability. Interoperability comes into play when two or more entities exchange information and use the exchanged information [25]. Research has been done to address this issue based on the current CAD technologies (for example see [26]); however, the emergence of more advanced technologies will introduce higher levels of interoperability which requires more research.

As a final challenge, we refer to the possibility of robots controlling over humans. Due to the rapid growth of artificial intelligence (AI) and automation, it could be predicted that the next generation AI can even take on more cognitive roles such as supervising and managing human workforce [1]. Thus, those in academia will need to research ways to control the learning of autonomous systems to avoid their domination in the future.

## Conclusions

In this report, we presented three factors that BioX, an artificial organ producer, will need to consider in order to become a leading global manufacturing enterprise in the year 2035. These factors include incorporating the infrastructure of industry 4.0, deploying advanced technologies in bioprinting functional organs, and implementing a green manufacturing paradigm to reach sustainability and be more environmentally responsible. Finally, some of the partnerships BioX will need to make are discussed and future challenges it may face are posed.

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