Available online at www.sciencedirect.com

ScienceDirect

IFAC PapersOnline CONFERENCE PAPER ARCHIVE

IFAC PapersOnLine 51-11 (2018) 1442–1447

Additive Manufacturing Plant for Large Scale Production of Medical Devices: A Simulation Study

Giuseppe Avventuroso*, Marco Silvestri*,, Enzo Morosini Frazzon*****

* Department of Engineering and Architecture, University of Parma, 43124 Parma (Italy)
(Tel: +39-0521 905700; e-mail: avventuroso@ied.unipr.it, marco.silvestri2@unipr.it).
** Department of Innovative Technologies, University of Applied Sciences of Southern Switzerland (SUPSI)
*** Industrial and Systems Engineering Department, Federal University of Santa Catarina, Florianópolis, Santa Catarina

Abstract: The capability of additive manufacturing (AM) to produce one-of-a-kind products makes it suitable to medical and pharmaceutical devices production, enabling the large-scale implementation of the personalized medicine paradigm. In this paper, to support planning, designing, and performance evaluation of an AM plant for large scale production of medical devices for healing chronic wounds, a simulation-based analysis was performed. Obtained results support planning and design decision-making, allowing for a better choice among alternative set-ups, and contribute to the evaluation of potential benefits and economic feasibility of new AM technologies.

Keywords: Discrete event simulation, Additive Manufacturing, Simulation-based Optimization.

1. INTRODUCTION

Nowadays dynamicity, due to the large progress in technology, globalization, customization and product complexity, has an enormous influence on the behaviour of every single company, and represents the modern challenge that enterprises have to face with. Many believe, in this booming context, that the rise of additive manufacturing technology will shape the future of production and help to liberate the established engineering and manufacturing processes (Giberti et al., 2017). With the dawning of the fourth industrial revolution, smart manufacturing and connected data are industry terms that are becoming increasingly important to the continued success and competitiveness of today's global manufacturer. Moreover, the transition from rapid prototyping to large-scale production of additive manufacturing machinery (AM) is generally regarded as an opportunity to increase the value generated during the manufacturing phase of a product life cycle (Holmström J. et al., 2010). According to experts, across all sectors the pharmaceutical one appears to have in particular the potential to better benefit the "next great step" involved in using additive manufacturing technology enabling fabrication of specialty drugs and medical devices (Elviri et al., 2016). The potential high impact of personalization in the Pharma/Medical fields is tied to one of the main challenges the modern medicine is facing, which consists in developing customized therapies.

Moreover, there is a strong and clear need for more flexible, reconfigurable and modular production facilities, in order to respond efficiently to dynamic demand, supply chain and current legislation (Baykasoglu, 2010). Additive technology is a natural response to the world market evolution, which nowadays puts more attention to the concept of customizability. Indeed, companies have to adapt to the environment in which they operate, to be more flexible in their operations and to satisfy different market segments (Ali M., 2014). In general, the field of the biomedical industry is the production sector where AM, also known as 3D printing, is used more widely. In 2012, medical applications accounted for 16.4% of total revenues for AM applications (W. Associates, 2013). One of the main reasons is that the capabilities of this technology are aligned with today's requirements of the medical reference segment. In order to optimize the treatments, today's medicine uses the newly discovered genetic information to adapt each drug to each specific patient. What sets the link between genes and diseases is called biomarker, which is a general term used to denote DNA sequences, the presence or absence of pharmacological receptors and the levels of some enzymes. Biomarkers will point out how to treat each patient in a stand-alone logic and not just on the basis of the disease they share (FDA, 2015). This new trend takes the name of personalized medicine.

Additive technologies are economically valid in those productive sectors which, by their nature, operate with small batches of complexes objects. In addition, additive production allows a deep change in the production chain, modifying the roles of the actors and proposing new business models. Moreover, the whole supply chain must turn itself into a more responsive structure in order to cope to the quick demand changes (Avventuroso et al., 2017). This change will bring opportunities and challenges to the world industry, allowing flexible and localized production close to the users. Reaching a more distributed production means to have a supply chain characterized by smaller costs associated to its smaller length and consequently its lower risk levels. In addition, adopting a decentralized production allows to arrange the production stations (3D printers) closer to the final users. Therefore, the production system used, directly affect inventory levels and the supply chain lengths and risks. A decentralized model requires less inventory and a shorter

10.1016/j.ifacol.2018.08.312

supply chain as it is closer to the customer, reducing the risks associated with bullwhip effect. In this framework, despite the improvements in terms of facilities' management and overall productivity, the operational performances of Pharmacological industry (inventory stock level, processes quality and service level) are worse than others industrial sectors (Ventola, 2014). In general, taking into account the processes quality and repeatability, most pharmaceutical companies works in levels between three and four sigma, using a centralized production model that comprise Supply Chain length about one or two years (Schubert C., 2014). More in detail, by introducing continuous production logic, it is possible to reach an improvement, in terms of production quality, close to five sigma level and, at the same time, to reduce the Supply Chain length and consequently the stock levels of the entire pharmaceutical industry (Ventola, 2014). In regard to adopted methods, simulation is seen as a tool of primary importance to obtain a better knowledge of system behavior (F. H. Hajihosseini, 2009). It allows to understand the system from an analytical point of view, which can hardly be otherwise reached. In addition, a research conducted by Jahangirian et al. (2010) shows that the DES methodology is the most used way in business and manufacturing analysis.
In this context, this paper performs a simulation-based analysis to support planning, designing, and performance evaluation of an AM plant for large-scale production of medical devices for healing chronic wounds. The paper is structured as follows. First section provides an introduction, section 2 presents the specific case study description. Section 3 presents the developed simulation model, section 4 includes the simulation results, section 5 is about the optimization process and finally the section 6 comprises the conclusion of the paper.

2. TEST CASE

This work aims to propose a new manufacturing concept for the production of specific biomedical devices. In particular, the product focus of this work is a 3D-printed scaffold for allowing tissue regeneration. It is an innovative 3D printed tissue repair material, conceived to drive healing of hard to heal chronic wounds by a bio-resorbable chitosan-based dressing. Specifically, this work analyses the potential use of 3D printing technology as industrial production tool considering a variant of the LFDM (liquid frozen deposition manufacturing) technology. From the production point of view, a scaffold can be defined along its dimensional parameters:

- Thickness of the layer.
- Diameter of fiber.
- Space between fibers.

In summary, the CAD (Computer-Aided Design) design of 3d-Printed scaffold is shown in Fig.1.

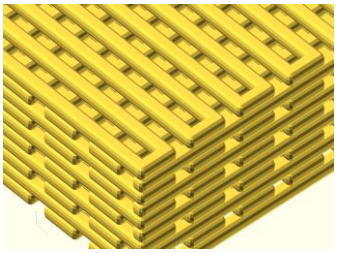

Figure 1: scaffold CAD design (Elviri et al., 2017).

Due to the specific challenges that a biomedical production must to address in terms of sterility and respect of FDA guidelines, the pilot plant is structured through the use of different cleanrooms. In particular, the entire line consists of five controlled environments for each production steps. The entire manufacturing process is structured following a specific process flow, as shown in Fig. 2.

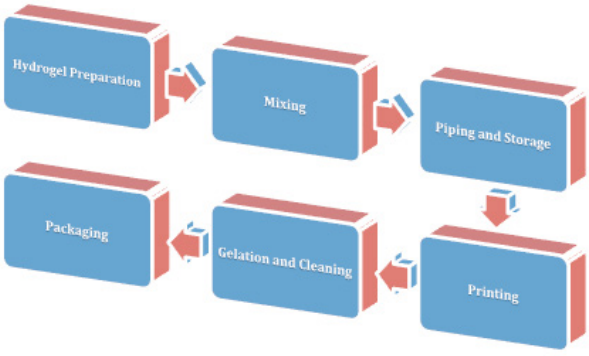

Figure 2: Process flow-chart.

The Hydrogel preparation is the first production stage (Elviri et al., 2017). Once the active ingredient arrived, it is first of all sterilized externally and then opened and weighed. The active ingredient, chitosan in the specific case, is introduced into the system in the form of powder, therefore, based on the real amount measured, the quantities of the other elements that make up the final solution will be determined. In particular, the Hydrogel will be obtained from a weighted combination of chitosan, acetic acid, raffinose and distilled water. Once obtained, the compound, output of the previous activity, is moved to the **mixing** stage. This operation is extremely important because it allows the homogenization of the entire compound and the achievement of target viscosity, suitable for processing by extrusion 3D printing technology. Once the mixing is started, the gel will stand in the machine for the next 24 hours before being used in the next step.

Once the mixing is over, the hydrogel is transported to a **storage tank**. It allows to keep the gel under optimum conditions in order to be printed, ensuring the respect of temperature and humidity constraints. Its goal is to provide the raw material to all the printing machines. In addition, this stage of production allows to create a buffer for 3D printers. Through the proper management of the production cycle, it will be possible to optimize the whole production according to the principles of continuous production. In other words, analysing and optimizing the idle time of the gel production

phase and especially of the mixing phase, makes possible to optimize the entire line, thus balancing the production stations with the aim of maximizing their saturation.

The next step is the **printing** phase. It is the real production stage in which scaffolds are printed by extrusion. In particular, every printer, taking the gel continuously throughout the printing phase, will produce the product by depositing the material on a specific metal base that, when print is over, will follow the workpiece until the end of the production process. In addition, the printers are grouped in cluster. Each cluster, composed by four printers, works into a separate cleanroom.

Once the piece is printed, it is moved with its base at the **gelation and cleaning** station. The printed structure, in order to solidify and stabilize, is subjected to basic solution jets. This process, one hour long, precedes the cleaning phase. This, through the dispensing of distilled water, aims to clean the product so that it can be processed by the next station.

The last production step is the **packaging** phase. Here arrive the printed pieces, already gelled and washed. The goal of this phase is to contain each scaffold into a polypropylene film, in order to provide also their primary packaging and thus refute any possibility of contamination of the object just produced. In particular, each scaffold will be stored in a packaging containing an aqueous solution. This allows to preserve the product over time, in terms of hydration, thus keeping it in the optimum conditions for transport.

Finally, the production process includes some manual activities. In fact, the system throughput is low enough to prefer a manual management of production to a fully automated one. In fact, by considering only to satisfy the 30% of the Italian demand, a throughput of 190 product per day has been defined. The operator manually loads each base whenever a printer is about to start printing. In addition, all the handling operations, in order to move the scaffold from the printing to the gelation station and from here to the packaging station, are carried out manually. In particular, for these movements, a Rapid Transfer System (RTS) is used. Finally, operators will provide the sterilization of metal bases, which will periodically be subjected to decontamination through autoclave. Finally, a skilled worker will carry out the weighing and preparation activities of the compound. The overall production line scheme is shown in Fig.3.

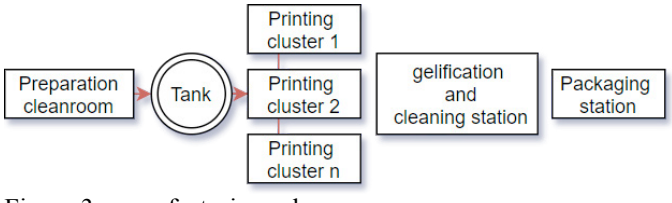

Figure 3: manufacturing scheme

3. SIMULATION STUDY

In this section, the simulation model realized through the use of the software application "Anylogic" (version PLE 8.1.0) is presented. The main objective of the simulation model is to emulate the operating behavior of the production system. In this regard, the first step was to define performance indices, on which the goodness of the solution found will be evaluated. Specifically, the chosen parameters are the entire production line capacity and the saturation of equipment and resources. Therefore, the chosen indicators are: throughput, saturation of human resources, gelation station and printing clusters. In general, it is extremely important to create a model that has an adequate level of detail (D. T. Sturrock, 2009). In this sense, the model has been realized considering some assumptions:

- Each product follows the same strict operation sequence,
- Each printer can perform only one operation at a time,
- The scaffold has constant dimension,
- The storage tank is considered always full,
- The order list is introduced only at the beginning of the simulation;
- Manual movements are carried out at constant speed,
- The operational speed of equipment, except for printers, is constant.
- The time needed for extraordinary maintenance, to be done manually, within each cluster whenever a failure event occurs, is considered constant.

The first step was to define the statistical distribution of the sample of data related to printing times. The 3D printers, focus of the following work, have been developed within the academic context of the University of Parma and therefore, it was possible to collect a sample of printing times that was sufficiently populated to have a statistical significance. However, any additive production process is heavily influenced by external factors such as air humidity, air currents, ambient temperature, hydrogeological composition, manual operations, and print-out features. This causes the printing process to be characterized by a certain degree of uncertainty, which, though minimal, is likely to affect the probability of failure of the process itself. Once the data sample was collected, a chi-square goodness-of-fit test has been applied to define its statistical distribution. In summary the simulation model inputs are shown in the following table.

Table 1. Simulation input

Input	Value	
Printing times (normal distribution)	Mean (minutes)	St. Deviation (minutes)
	240.83	12.37
Gelation duration	1 h	
Cleaning duration	10 min	
Defect rate	1%	
Manual handling speed	1 m/s	

RTS capacity	5 products
Gelation station capacity	10 products
Scaffold dimension	100 x 100 x 1 mm
Simulation time	24 h
Maintenance time	10 min

Based on what has been described in the preceding paragraphs, the simulation model has been realized according to the logic shown in the following figure.

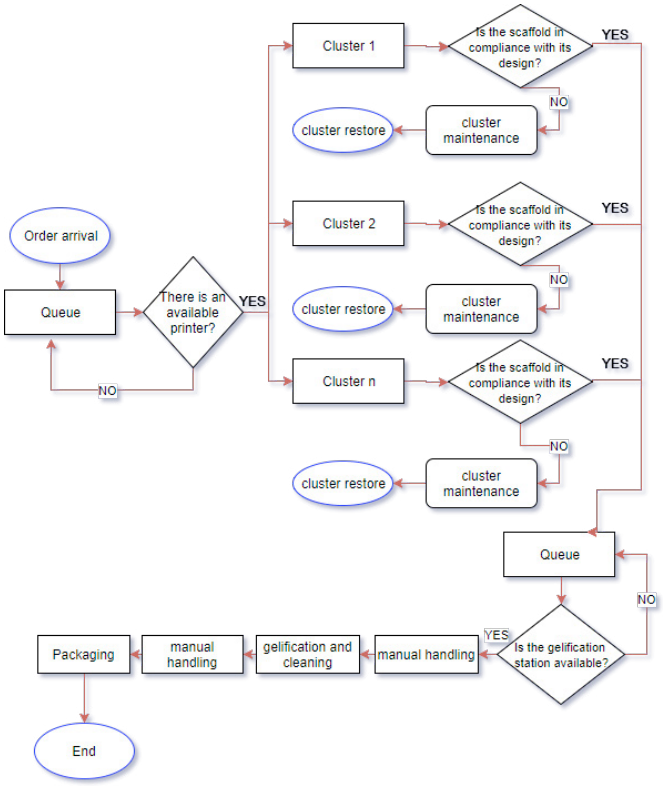

Figure 4: simulation conceptual model

4. SIMULATION RESULTS

As previously mentioned, the goal is to study the system behavior and understand how it is able to cope with the design requirements. Therefore, the first step was to test the model with the starting production scenario. In particular, reference is made to the line configuration obtained using the following variables:

Table 2. Starting scenario

Variable	Value
Number of printers	40
Number of clusters	10
Number of employees	1
Number of gelation station	1

Based on inputs and variable already defend, system outputs were collected. In particular, according to the objectives of this work, it was decided to evaluate the system according to five different parameters:

- Printers saturation,
- Number of wasted products,
- Employee saturation,
- Saturation of the gelation station,
- Throughput.

Therefore, the results of the scenario being analysed are:

Table 3. Simulation results

Parameter	Saturation
Printers	95%
Employees	28%
Gelation station	98%
Parameter	**Amount**
Wasted product	2
Final product	230

Based on the collected results, different considerations can be drawn, such as the high saturation for both printing and gelation stations.

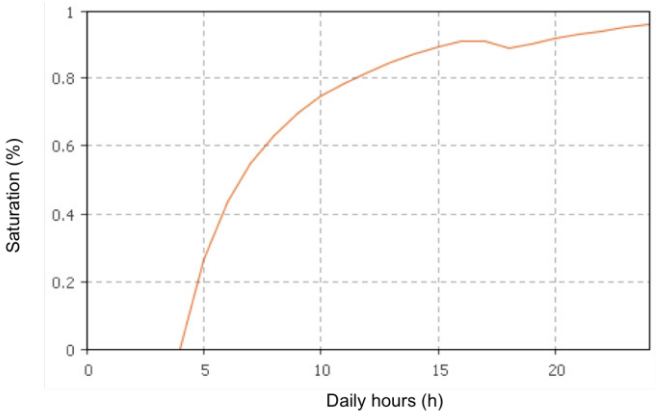

Figure 5: daily gelation saturation

Normally, at the design stage of a new production line, one of the goals is to create a concept that allows high saturation of machines. Nevertheless, an excessive saturation means increasing risk situations. In fact, it is useful to think a production configuration that allows, a high exploitation of resources, but in the same time a margin of safety which, in the case of particular events, such as extraordinary maintenance, allows to split the production from one station to the other without compromising the operational continuity and the achievement of the required production. Further, based on the above results, it can easily see that the gelation station is the bottleneck of the whole line. In addition, by forcing the system within the range of its variables, this phenomenon is more evident. More in details, stressing the model in order to realize more scaffolds, it can be noticed that the product amounts remain unchanged, since the gelation station can not satisfy the demand for use of the considered scenario. However, the achieved throughput meets the minimum production requirement of 190 pieces per day. Moreover, employees' saturation, well under the legal

limit, ensures a safety margin to address with eventual unexpected events.

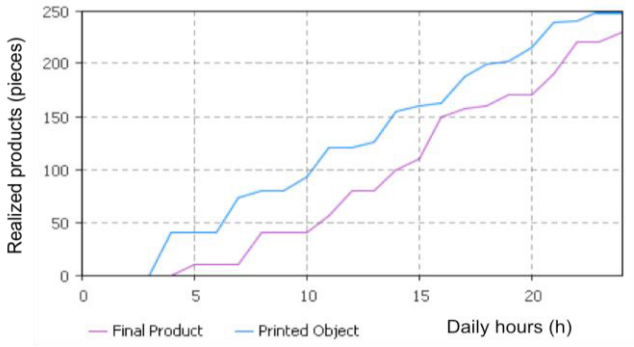

Figure 6: daily throughput

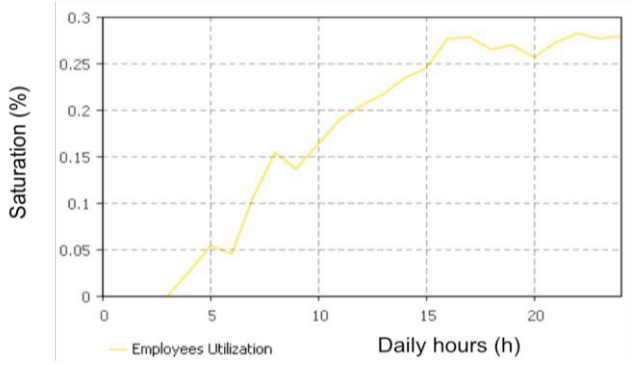

Figure 7: daily employees' utilization

As shown in the previous figure (fig.6), there is a significative difference between the number of printed objects and the number of final products. More in detail, the workstations, downstream of the printing's one, are not able to process the effective quantity of printed products. Moreover, taking into account the huge cost of each facilities working into a controlled environment, there is the need to define the best configuration that balances throughput and the investment costs. For this purpose, an optimization process through simulation has been carried out.

5. OPTIMIZATION PROCESS

The optimization process carried out in this study is classified as a ranking-and-selection (R&S) problem. In that framework, the study plans to simulate all possible solutions and select the best among them. In particular, the purpose is to find the solution that allows to cope with demand needs and that corresponds to the minimum initial investment. In particular, process controlled variables and their allowable ranges of values are shown in the next table.

Table 4. Optimization process variables

Variable	Range	
	Min	Max
Number of printers	20	40
Number of gelation station	1	3
Number of employees	1	5

Based on the economic quotations of each production environment and machine the following objective function has been defined:

$$\min[(k_1 * a_p) + (k_2 * a_{iso,pr}) + (k_3 * a_{gel}) + (k_4 * a_g)]$$

Subject to constraints:

$$FP \geq 190$$
$$1 \leq a_p \leq 40$$
$$1 \leq a_{gel} \leq 3$$
$$1 \leq a_h \leq 5$$

Where FP is the amount of final product actually produced, Ap represents the number of printers, Ah is the number of workers, $Agel$ represents the number of gelation stations, and finally $Aiso$, pr is the amount of printing clusters. In addition, $k1$, $k2$, $k3$ and $k4$ are respectively the investment unitary costs associated to printers, cleanroom for printing clusters, gelling units and daily cost of a worker.

Taking into account the mathematical formulation above discussed, the line configuration, corresponding to the optimum solution encompasses:

Table 5. Optimum line configuration

Variable	Value
Number of printers	36
Number of gelation station	1
Number of employees	2

This line setting, able to produce 210 products per day, allows to significantly reduce the investment costs achieving at the same time a throughput greater than the minimum required. In addition, as shown in figure 8, with this solution it is possible to reach high gelation station saturation. More in detail, the station, used about the 80 % of the time, reduces the potential risk, associated to unexpected events, compared to the starting configuration.

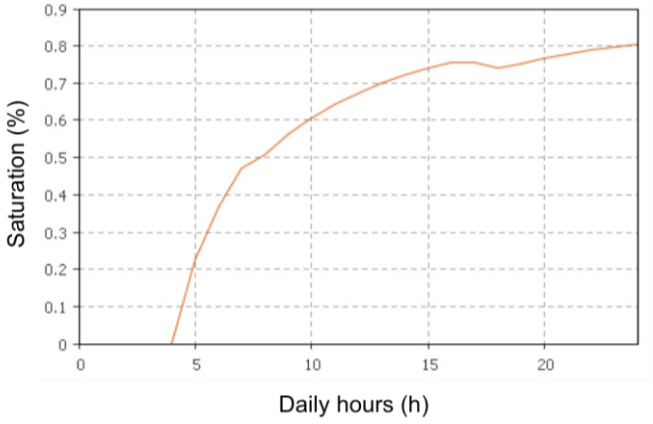

Figure 8: daily gelation saturation, optimum solution

The use of two employees results in a lower utilization of the resource pool. Nevertheless, adding a resource it is possible to increase the total production about the 12% thanks to the reduction of waiting times for manual movements. Moreover, having more resource "on field" gives a high flexibility rate. In fact, it is possible to cope with simultaneous maintenance or gel preparation tasks

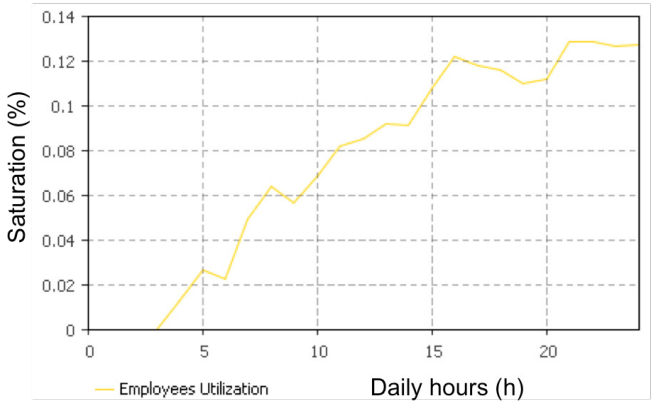

Figure 9: employees' saturation, optimum solution

6. CONCLUSION

Flexibility and customizability are both relevant trends in manufacturing systems, pushed forward by market demand and growing competition. Among other technologies that are able to cope with these challenges, additive manufacturing and 3D printing stand out. Indeed, in this work a practical case, in which 3D printing technology is the solution to realize new objects hardly achievable with other technologies, has been discussed. Moreover, one of the most promising sectors for their utilization is the pharmaceutical one. Therefore, an innovative production system for 3D printed medical devices has been shown.

However, in order to convert innovation potential into real application and economic returns, these emerging technologies must prove to be efficient and reliable. Indeed, the proper consideration of afore mentioned characteristics means coping with several challenges, since some constraints are often difficult to be described by traditional analytical models. In this direction, this paper proposed a simulation study for the operational and economic evaluation of a pharmacological production system based on additive technology. More specifically, the simulation-based evaluation targeted on obtaining the production line throughput considering different resources configurations and constraints regarding processes and demand. Thereof, this research substantiated the applicability and suitability of additive manufacturing technology in pharma framework. Furthermore, the developed simulation procedure has turned out to be an interesting tool to emulate in a faithful way the 3D printing process behaviour. The test case provided insights regarding the potential industrial application of a production systems based on 3D printing technology. Several simulation runs have been executed, in which input parameters of the model were changed according to different resource allocations. In particular, a ranking-and-selection optimization process has been carried out in order to find the optimum solution balancing the throughput and the investment costs.

Future research topics are mentioned below:

(i) development of a simulation model based on a networked multi-batches processing; (ii) simulation-based evaluation of orders scheduling approaches based on the demand and its specific customization features coming out directly from customers´ specification.

Moreover, further studies should take into account the integration with ERP systems, with the goal of managing the entire contract lifecycle, from digital order arrival until physical order delivery.

REFERENCES

Ali, M. A.Z. (2014). A simulation study of FMS under routing and part mix flexibility. *Global Journal of Flexible Systems Management*, 15 (4), 272-294.

Associates Wohlers (2013). Additive Manufacturing and 3D printing: State of the industry. *Annual Worldwide Progress Report*, 14

Avventuroso, G. et al. (2017). A Networked Production System to Implement Virtual Enterprise and Product Lifecycle Information Loops. *IFAC-PapersOnLine,* 50 (1), 7964-7969.

Avventuroso, G., et al. (2017). Production paradigms for additive manufacturing systems: A simulation-based analysis. 2017 ICE/ITMC, pp. 973-981 doi: 10.1109/ICE.2017.8279987

Baykasoglu, A.,G.K. (2010). Capability-based distributed layout and its simulation based analysis. *Journal of Intelligent Manufacturing*, 1-13

Elviri, L., et al. (2016), 3D-Printed Polylactic Acid Supports for Enhanced Ionization Efficiency in Desorption Electrospray Mass Spectrometry Analysis of Liquid and Gel Samples, Talanta (155) pp. 321-328, doi: 10.1016/j.talanta.2016.05.010,

Elviri, L. et al. (2017). Higly defined 3D printed chitosan scaffolds featuring improved cell. *Biomedical Materials*, (12).

FDA (2015). What are "biologics" questions and answers.

Giberti, H.; Sbaglia, L.; Silvestri, M. Mechatronic Design for an Extrusion-Based Additive Manufacturing Machine. Machines 2017, 5, 29. doi:10.3390/machines5040029.

Hajihosseini, F.H. (2009). Importance of Simulation in Manufacturing. *World Academy of Science, Engineering and Technology*, 285-288.

Jahangirian, M.E. (2010). Simulation in manufacturing and business: A review. *European Journal of Operational Research*, 1-13.

Schubert, C. (2014). Innovation in 3D printing: a 3D overview from optics to organs. *British Journal of Ophthalmology*, vol.98, n.2, pp. 159-161.

Sturrock, D. T. (2009). Tips for successful practice of simulation. *Proceedings of Winter Simulation Conference*, 34-39.