The Designing Process for a HMES Used for the Management of Radiopharmaceuticals Production

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Abstract. This paper discusses the design, implementation and validation of a management system for radiopharmaceuticals production based on a reference Holonic Manufacturing System (HMES) architecture. Starting from the PROSA reference architecture our main goal is to design an integrated platform for resources management, production scheduling, manufacturing process control and data traceability and storage. All these operations have to be performed and monitored according to latest nuclear safety standards and environment regulations. The paper shortly presents the particularities of radio-isotopes pharmaceutical production inside a specific nuclear facility and proposes a HMES system design that could be easily adapted for any type of facility, since the manufacturing workflow and the production's environment conditions are similar.

Keywords: Holonic manufacturing · Semi-heterarhical control · Radiopharmaceuticals production · NetLogo simulation

1 Introduction

Radiopharmaceuticals are an established tool for key investigations in numerous disciplines of the life sciences and for diagnosis and treatment of many life threatening diseases. Produced using a cyclotron and dedicated radiochemistry equipment and laboratories, those products are used for positron emission tomography (PET) and single photon emission computed tomography (SPECT).

The main challenges of the radiopharmaceutical facilities are to manufacture valid nuclear medicine products in the shortest time possible and in a safely manner for the employees and surrounding environment. They are specialized in producing a small set of products in small volumes, according to the demand of hospitals and PET centres. Even having a specific chemical structure, radioactivity and usage, each product follows the same production path: radio-isotopes are produced in a particle accelerator (cyclotron), transferred after into technology isolators for chemical synthesis and vial dispensing, passing through quality check laboratory for conformity tests and in

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the last stage, final products are packed and transported to the clients in shielded containers. A typical radiopharmaceutical product workflow is presented in Fig. 1.

The preparation of radiopharmaceuticals requires a safe, clean and aseptic workplace. Special environment conditions must be fulfilled continuously during the manufacturing process. These conditions could be divided in two main categories: radioprotection safety conditions (radioactivity doses, pressure cascades and air change cycles) and environment manufacturing conditions (temperature, humidity and pressure, number of particles) as defined by GMP[1], guide or recommended by IAEA[2] in their technical reports [1].

The automation of manufacturing processes and environmental monitoring is present only at local level: every equipment has its own PC running dedicated control software forming a couple of "automation islands" [2]. Data sharing between islands and with the entire manufacturing system represents a difficult task due to the different standards and automation platforms involved.

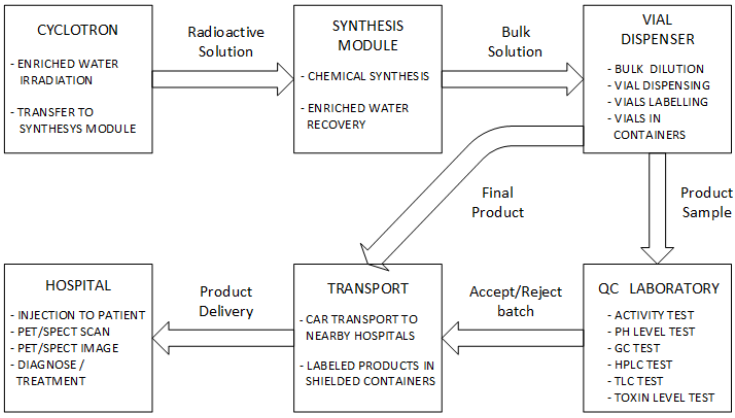


Fig. 1. The workflow of a radiopharmaceutical product from cyclotron to hospital

The process data or the test results are locally stored or printed. Therefore comes the need for an integrated software solution for managing the internal logistic of the production and the big amount of process and environmental data. For the Quality Control (QC) Laboratory, the software must provide Laboratory Information Management System (LIMS) functionality [3]. A LIMS will provide the effective monitoring and recording at the batch level, creating records that trace the path of the products as they are passing from production stages to packaging. While most of laboratory work has often been done externally from the LIMS, instrument-to-LIMS interfaces are now being developed by manufacturers. Such interfaces allow raw data to be imported directly to the LIMS, which then can store, process, and report all the information for analysis [4].

[1] GMP : Good Manufacturing Practice.
[2] IAEA: International Atomic Energy Agency.

A successful attempt has been made in automating the entire radiopharmaceutical production process using a PLC controlled system [5]. However, the tested architecture has the following drawbacks: the manufacturing process is product specific, no supervisory system for perturbation or failures is present and QC routine check of the final product is missing. Our proposed software architecture intends to cover all the production's stages and aspects as required by GMP.

The application of holonic concepts to manufacturing is motivated by the inability of existing manufacturing systems to deal with evolution of products within an existing production facility and to maintain a satisfactory performance outside normal operating conditions [6]. The term holon was chosen for capturing the dualistic capabilities of autonomy and cooperativeness within a single entity. The concept was found suitable to encompass the entities, physical as well as abstract, in manufacturing control and management [7]. The strengths of a holonic organization are represented by the efficiency in the uses of resources, the high reactivity due to decentralization, and the adaptability to change in their existing environment.

The reference architecture for manufacturing, PROSA is built around three types of basic holons: product, resource and order control: recipes or process plans, resource handling and internal logistics [8].

The remainder of the paper is structured as follows: section 2 the radiopharmaceutical manufacturing process and the building block of the software application; section 3 details the structure of the HMES system and section 4 details its functionality; section 5 contains the simulation of the manufacturing process. Conclusions and future challenges are presented in section 6.

2 Radiopharmaceuticals Manufacturing Process and Core Components of the Management System

The radiopharmaceutical manufacturing process has a typical flow-shop structure and starts when a client's order is received and the entire facility (machines and human personnel) is ready for operation. The first step of production is represented by the enriched water irradiation using a cyclotron. The radioactive water is then transferred inside a technology isolator, where a chemical synthesis module mixes chemical reagents from a cassette to obtain the product bulk solution. Next, the vial dispenser is calculating the required product quantity and activity for each vial, according to client's order. A sample from the product batch is sent to QC laboratory and after running a series of test methods on analytical instruments, the laboratory confirms the product's dispatch to hospitals or rejected the entire product batch for non-conformities. Since radiopharmaceuticals are based on short-lives radioisotopes (between 109 min. and 360 min. half-time[3]) an important goal of every facility is to ensure that the production timeline is strictly respected. The products must reach the hospitals in the right time and with the specific requested activity. Orders for different

[3] Half-time: the time period after the number of element's atoms and activity is reduced to half its value.

types of products are executed in separate production batches to avoid the risks of cross-contamination [9].

The production process must be supervised by an environment monitoring system as all the production stages are environment dependent. The air quality in the production area and the radioactivity levels must be continuously monitored together with physical environment parameters. After production, the recorded logs must be stored for reports and for further batch audits. Alarm and action limits are defined for each environment parameter and provide a useful tool in taking real-time corrective action or critical decisions (production stop or delay) in case of perturbations.

Aiming for multidisciplinary information and application integration, we propose a production management system based on the following core components:

- *A web based application* to access the database information and confirm, reject or postpone in real-time a client order for a specific product. A graphical user interface will provide access over internet and non-proprietary OS based access to stock list and facility resources needed for manufacturing the requested product.
- *A production scheduler* based on time constraints imposed by radioactive decay of the radionuclides contained in products and personnel, machines or other resources availability. The scheduler will calculate if a new order can be done in the required time or planned orders parameters can be adjusted to obtain the new demanded products from the same batch.
- *A process monitor module*, enabling the facility's supervisor to have an overall view of the production area and its environment. This module will bring real-time information about the manufacturing stages of the products, production room environment and radiological monitoring system. Collecting all the data from radiation detectors in a live chart, this module will provide the supervisor the exact location of the product at any time. Warnings can be received in case of machines or operations failures, permitting corrective actions to be taken in useful time.
- *A product tracking module*, will gather all the information about the raw materials the product is made from or single-use materials (cassettes, gloves, needles) that came in contact with product during manufacturing process. If non-conformities or microbiologic contamination are detected during quality check tests the tracking module can search its labels barcode database to provide the product component list.
- *A data storage module* in a Historian Database will provide a useful tool for process data analysis, process optimization and for generating complete production reports. Production batch records must be stored for at least 2 years (according to GMP) and must be available all the time for inspectors and audit procedures. Gathering different data in various formats from independent machines and storing them in a common format will be the main advantage provided by this module.

A centralized management system represents the optimal solution for data exchange and access. In the production scheduling process, shorter production times are obtained as high level planning algorithms are used [10].

3 The Proposed HMES Architecture

Starting from PROSA basic holons defined in [11], we will introduce the design of a HMES management system, defining its architecture, types of holons, modules of implementation and functionality.

The disturbances that could frequently affect the manufacturing process (machines breakdown or running out of vital resources, improper environment conditions in the production area, product contaminations or high levels of radioactivity) must be taken in consideration both in the scheduling and in the production process.

The proposed system has a 3 layers architecture as represented on Fig. 2. At scheduling level, a web-based MES software will provide the link between the client orders and the production database. For every order received, the application will interrogate the database to find which resources, raw matters and human operators are available for executing the order in the requested timeframe. The estimated time for order delivery will be calculated by analysing the previously production process parameters stored in the database. If the orders can be completed in time, a confirmation will be sent to the client, and all the orders information will be passed to the management level, where basic PROSA holons and specific holons like Environment Holon, Time Holon or Operational Holon are structuring the data for the automation level. At this level, a PLC sends commands for the physical resources and reads data from them. A SCADA controller will read the environment parameters from the sensor network and provide information to the Environment Holon. In the same time, the recorded process data from PLC and from SCADA system are transferred to production database for storage, analysis and reports.

A customizable open-source MES application will provide the graphic interface for accessing the product models, available production resources and human resources, and the stock of raw matters and supplies involved in the manufacturing process. A product model contains the product recipe (raw matters, chemical reagents and the sequence of operations performed by resources, product physical and chemical specifications).

The Production Database is storing the production data, environment data and the process historian. Production data are composed by product models, resources list, raw material stocks, suppliers list, employees working program, process time list and delivery time list.

Environment data are represented by an environment model with a GMP defined set of rules for environment parameters (air quality, temperature pressure, humidity).

Product Holon (PH) is storing the information about a product type. Any type of products that can be manufactured by the nuclear facility and the resource setup is defined in the PH. This holon is in fact a theoretical description of a physic product, but not directly associated with it like the Resource Holon.[12]

Production Scheduler is in charge with scheduling of the entire production process (from the first stage of production until customer's products delivery). The scheduler is gathering all the needed information from the Product Holon, Resource Holon, Time Holon and Opera Holon and launch and track the execution of the Order Holon.

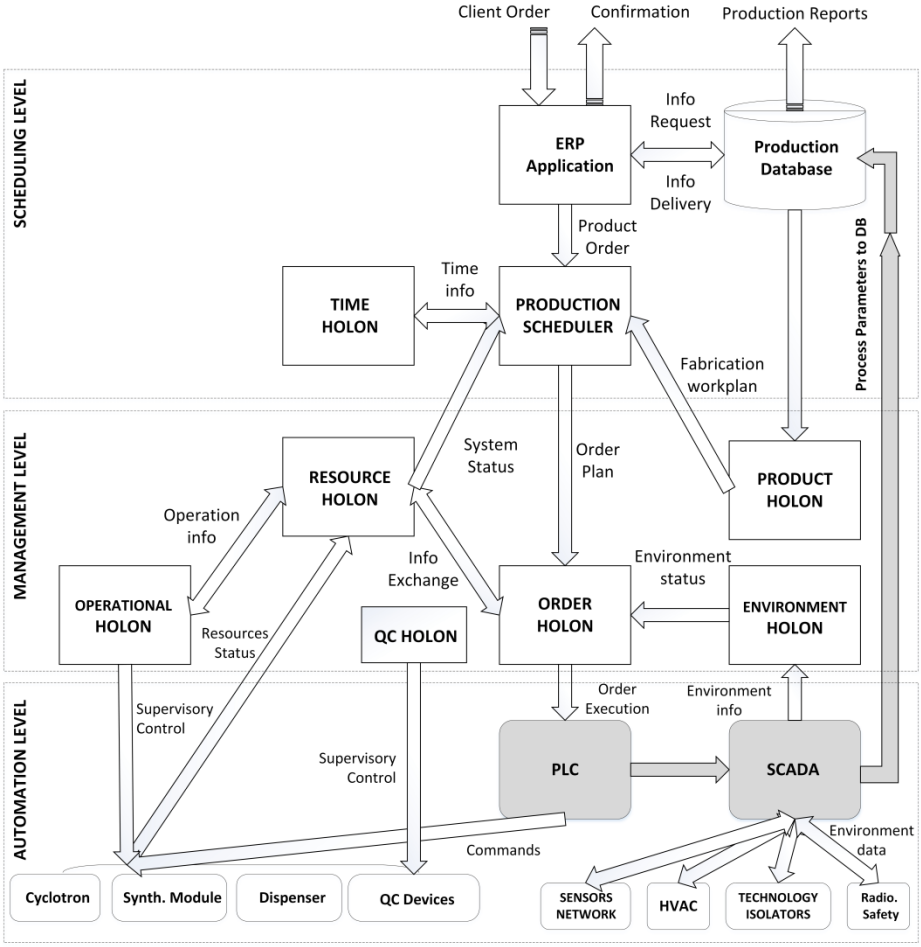


Fig. 2. The 3 layers architecture of the HMES management system

Resource Holon (RH) is storing the information about manufacturing resources (cyclotron, technology isolators, synthesis module and quality control devices).

During the manufacturing process, the RH is providing resources working status and load information. In a nuclear facility we encounter two main types of resources: fully automated and human operated resources.

Operational Holon (OPH) is storing the information about the human operators. It possessed the same level of knowledge as a trained operator for a specific resource. Its role is not only to assist the human operator in taking a decision (like Staff Holon in PROSA), but to replace him when needed. Actions like setting up a resource for work or a visual inspection of a product test can be easily implemented by hardware-software modules.

Time Holon (TH) is storing the information about the delivery times for each client. It contains a predefined schedule for the working days, and stores values for

the transport times according to car traffic at different hours. Production Scheduler must take in consideration these values to avoid losing to much product activity on the on the way to hospitals. If a product could be manufactured on time by the production line but it can't be delivered on time to customers the order will be re-scheduled.

Order Holon (OH) is storing all the necessary information to produce one certain type of product. This holon is created only when a product order is entered into the system. The OH allocates all the resources needed for the product manufacturing and it holds the status of the unfinished product for every production stages.

Environment Holon (EH) is storing the information about the production environment. This holon is comparing the data received from the SCADA system with the Environment Model stored in the Production Database and notifies the Order Holon if environment condition are proper for radiopharmaceutical production. If perturbations occur during the production process, the Order Holon will decide if the product has been compromised and it may cancel the entire batch execution.

Quality Holon (QH) is storing the information about the quality tests that must be performed for each product type, the test machines required to perform test operation and the analytical methods they will use for testing the product samples.

PLC is a programmable logic controller connected to all the manufacturing resources on the shop-floor line. PLC inputs receive instructions for order execution from the Order Holon and its outputs are sending control commands to the connected manufacturing resources. Status and operating parameters of the resources are read and transferred into Product Database for storage and reports.

SCADA system is in charge with environmental parameters monitoring. The system is connected to HVAC and technology isolators own measuring devices and also to the radiological monitoring system. This system is providing real-time data for the Environment Holon, warning the human operators if alarms level or action levels are reached and transferring the entire environment data intro production database for storage and reports.

4 HMES Functionality for Environment and Scheduling

Since the production process is strongly dependent both on facility's environment and technical isolator's internal environment, alarm levels and action levels are defined for each parameter stored in the environment model. Alarm level warns the SCADA system and the human operators (or Operational Holon) that one or more parameters are not in the desire range and requires investigative actions. Action level alarms require immediate corrective actions from the HMES. If the system is unable to restore the environment conditions in a given period of time, the production is delayed, but in the case of critical parameters[4] deviations an entire product batch is lost. Several methods of controlling the environment by adjusting the HVAC parameters in real time have been proposed and developed in [13] and [14].

[4] Critical parameters: number of particles < 0,5 and 5 μm (inside technology isolators) and radioactivity levels.

The launching of a product order by the proposed HMS is taking place in the following steps represented in Fig. 4. Step 1: An order for a specific product is received by the Production Scheduler. Step 2: Product Holon is contacted to check the product recipe. Step 3: Product Holon checks that all the raw materials and supplies are available and provide the resources list necessary for production. Step 4: Production Scheduler contacts the Resource Holon. Step 5: Resource Holon confirms the requested resources are available for work and they are able to perform the requested operations.

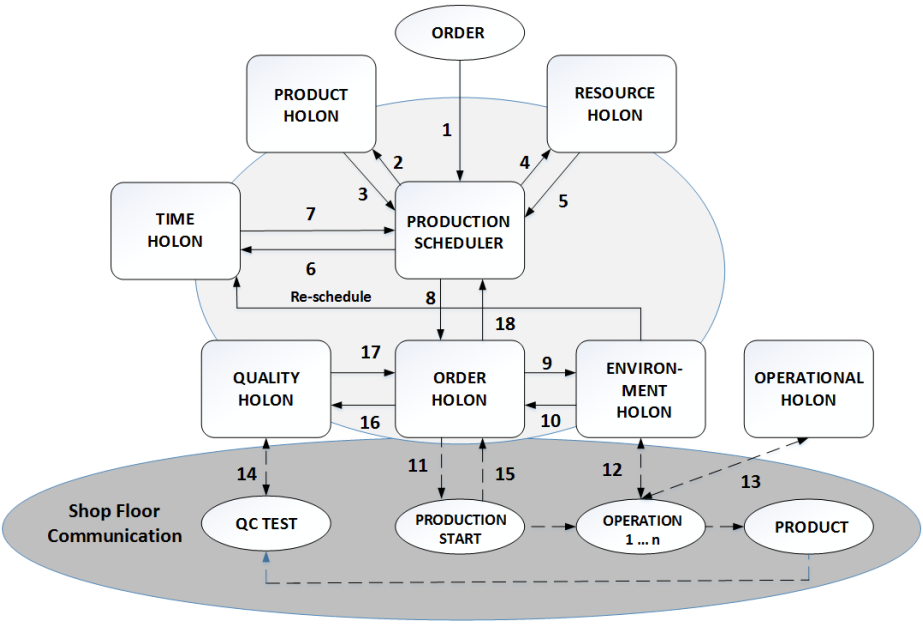


Fig. 3. The interaction between HMES holons for scheduling and order launching

It a resource is not available, it could be replaced by a backup resource. If human operators are not available, Operational Holon will perform their tasks. Step 6: Production Scheduler consults the Time Holon to check the order can be delivered in the required time. Step 7: Time Holon confirms the order can be done in the required time, otherwise the order is cancelled or re-scheduled. Step 8: Order Holon is created for the current product order. Step 9: Environment Holon is contacted before production start to check if all the required environment conditions are met. Step 10: Environment Holon confirms the environment is proper for production, otherwise delays the production start until all the parameters are according to Environment Model stored in the database. In this case Time Holon will be consulted to see if the order will fit on delivery time with this delay. Step 11: Production is initiated in the shop-floor level. Step 12: During operations executions, some resources are production environment changes (radiation levels, airflows). Environment Holon will track the changes and will analyse if they exceed the values from the environment model. If the

parameters can't be restored to the desired values in a required time, the production will be stopped. Step13: During production, some resources require human operators and dedicated control software. In case one operator isn't available to execute an operation or it may be too dangerous for him (radiation level), the Operational Holon can communicate with the control software and execute the operator's tasks. Step 14: The final product has been obtained in the last stage of the shop-floor. A product sample is sent to QC laboratory for conformity tests. Quality Holon will assign test devices and analytical methods for the product sample analysis. Step 15: Order Holon is being informed that the product has ended. Step 16: Quality Holon is contacted to confirm the product conformity tests. Step17: Quality Holon confirms all tests were successful; otherwise production is cancelled until the unconformity problem is identified and solved. Step 18: Scheduler is informed that the order has been completed.

5 Simulation of the Proposed HMES Using NetLogo

A HMES model for controlling the radiopharmaceutical production was developed in NetLogo. NetLogo world is, basically, composed by two types of agents, the stationary agents (patches) and the mobile agents (turtles). The patches are arranged in a grid way, so they can form the world in over that the turtles move around [15]. In the proposed architecture, the dot shaped turtle (the product) is passing the production line from the cyclotron to the transport car, and after that, to the hospital. The cyclotron, the two synthesis modules and the dispenser are examples of Resource Holons while the Quality Holon is represented by the analytical instruments performing product quality test (from 1 to 5). The Resources Holons are represented by white and grey patches. Product Holon is created with a process plan containing the details and sequence of operations that must be fulfilled. During its lifecycle the Product Holon will interact with the Resource Holon in order to guarantee a good product execution.

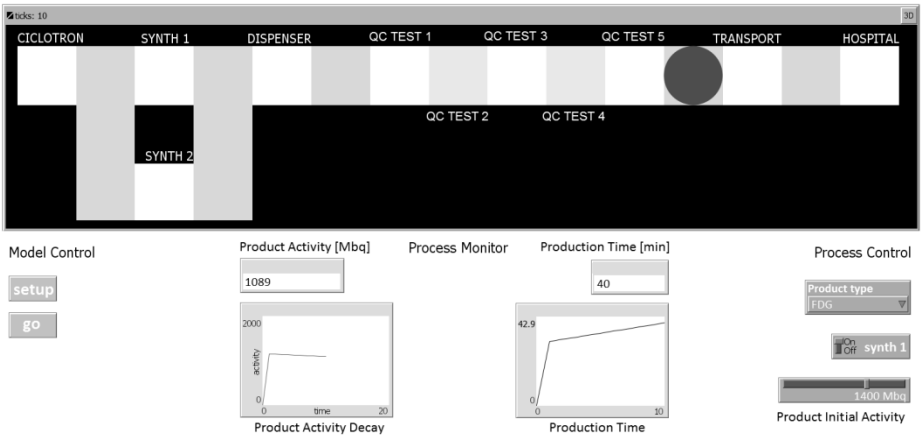
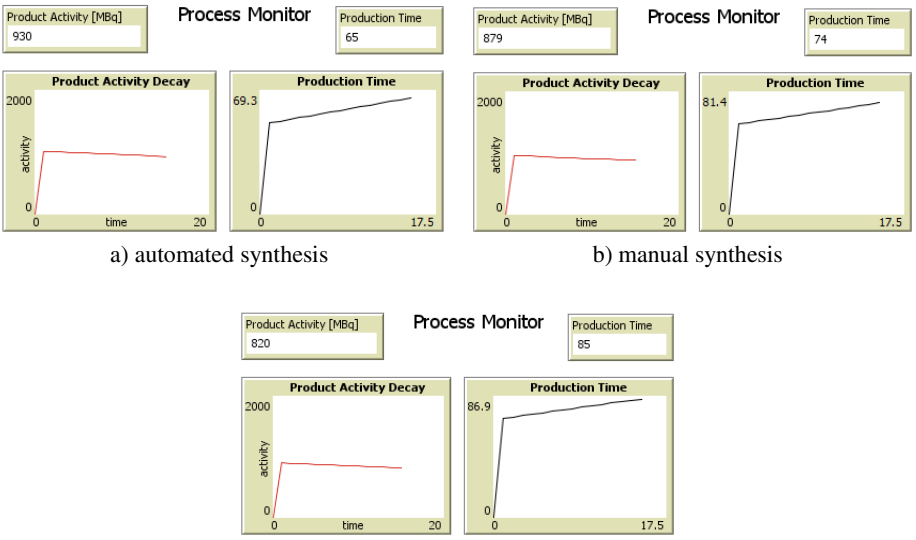


Fig. 4. NetLogo simulation of a radiopharmaceutical production line

Execution times for each resources and QC devices involved in production are stored and can be modified in the software program. Taking these values from the real experimental facility [16] the total production time and the final product activity can be calculated and compared for each type of product. The process control interface let users choose the product type and the product initial activity. Using radioactive decay law[5], the model can calculate the final product activity the hospital will receive. An on/off switch simulates the out-of-order state for the main automated synthesis module (SYNTH1). In this case, the production line will be switched to backup synthesis module (SYNTH2). An area to visualize the results was included, considering the graphical representation of the product activity and the production time.

Three scenarios were simulated for production of 18F-FDG[6]: production using automated synthesis module, production using the manual operated backup module, and a simulated failure in the Class A[7] dispenser environment (which induce additional 20 minutes recovery time delay). The results are shown in Fig. 5.



a) automated synthesis

b) manual synthesis

c) dispenser environment recovery

Fig. 5. Simulated results for the final product activity (MBq[8]) and total production time (min.)

[5] $A(t) = A_0 e^{-\lambda t}$ The final product activity depends on initial activity, time and λ decay constant.

[6] FDG is the commonly used radiopharmaceutical product.

[7] Class A : environment where the number of 0.5 μm particles/m^3 are less than 3500.

[8] MBq : megabecquerel. One becquerel represents one disintegration per second.

6 Conclusions and Future Challenges

In this paper it has been presented a Holonic architecture for managing the radiopharmaceutical production process. The main advantages that results from the use of holonic concepts are the centralized storage of various types of data and the implementation of the manufacturing process with autonomous and cooperative entities. The resulting system is a modular and flexible one and can be easily adapted for any other types of radiopharmaceutical facilities as a LIMS system with extended functionality. The real-time scheduling and the continuous environment monitoring represent key aspects in obtaining good quality products while minimizing the operator's exposure to radiation.

To assets the proposed holonic system design a simulation model has been implemented using NetLogo environment. Results obtained for different simulated scenarios are compared to reveal the importance of every minute for products based on short-life radionuclides. The current model could be updated with any types of radionuclide specification and machines operations timing, providing a useful tool for production scheduling. Simulated results can be also used to study if the real existing system is able to produce and deliver new radiopharmaceutical products.

Future research includes the implementation of all types of holons described in this paper. The work will focus on Environment Holon interaction with production holons using an environment model and on production's scheduling optimization using genetic algorithms.

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