Inessa Ainbinder, Application No. 2917/24

**Supply chain model of a decaying product – The case of radiopharmaceuticals**

1. **Scientific background**

Radiopharmaceuticals are a classic example of a decaying product. Radiopharmaceutical cyclotrons (RCs) are small supply chain (SC) systems that have several cyclotrons serving a network of customer hospitals. In the literature, we have encountered a lack of SC planning and scheduling models for decaying (or deteriorating) products, although we did find a few restricted models for RC systems. In this work, we intend to address this fundamental gap. Since an SC is a very broad type of system, one must focus such research endeavors on a specific type. Hence, we chose to focus our research efforts on the case of SCs for RCs, which are small SCs with rapidly decaying products.

The use of RCs is growing rapidly, and it is estimated that there are over 1,500 cyclotrons worldwide according to an International Atomic Energy Agency report from 2021. Radioactive substances are used in a variety of medical treatments [1]. In this work, we focus on the case of cyclotrons for radioisotope F-18 (with a half-life of 110 minutes), which is used for diagnosing and monitoring many types of cancers. As such, careful coordination of the production stages and timely delivery to the medical end-users are required [2]. Other examples of goods that deteriorate in value over time are fruits [3], certain chemicals, volatile liquids, and blood from blood banks. In general, deterioration can emerge because of physical decay, damage, spoilage, evaporation, approaching obsolescence, market value, or the end of a season [4, 5].

In 1913, Ford W. Harris [6] developed the economic order quantity (EOQ) formula, although Wilson is given credit for its application and in-depth analysis [7]. In the existing literature on inventory control systems, it is generally assumed that the lifetime of an item is infinite [8]. In real-life situations, this assumption is a reasonable approximation, but in various scenarios, it is not. Several researchers have focused their study on deteriorating items [9, 10, 4]. Ghare [11] developed an EOQ model for an exponentially decaying item with a constant demand rate. Several papers [12, 13, 14] proposed a model with variable deterioration using a two-parameter Weibull distribution. Misra [15] developed an EOQ model with a Weibull deterioration rate for perishable products without considering shortages. Tadikamalla [16] developed an EOQ model assuming the Gamma distribution for deterioration. Bhunia and Shaikh [17] developed two inventory models for deteriorating items with variable demand dependent on the selling price of the items.

Taft [18] was the first to develop the economic production quantity (EPQ) model. Another study [19] presented an EPQ model that includes exponentially deteriorating raw materials with a non-deteriorating product. Balkhi and Benkherouf [20] presented a production lot size inventory model for exponentially deteriorating items in which the demand and production rates are functions of time. Yang and Wee [21] develop a multi-lot-size production and inventory model of deteriorating items with constant production and demand rates. Widyadana and Wee [5] developed a deteriorating production–inventory model with random machine breakdown and stochastic repair time. Kim et al. [22] developed a lot-for-lot delivery model for an SC using returnable transport items for shipments. Chan et al. [23] presented an integrated production–inventory model for exponentially deteriorating items assuming constant demand and production rates. In this model, shortages are not allowed and shipments are immediate.

The production of radiopharmaceuticals is in the class of semi-continuous manufacturing processes characterized by continuous flows that are not run in steady-state mode [24]. This type of production line specializes in small batches of products in small volumes according to the orders received from hospitals. In such systems, the interaction of discrete and continuous processes requires hybrid control. This hybrid control includes a discrete event part for the supervisory control that communicates with the continuous plant [24]. Silisteanu et al. [25] presented an optimal radiopharmaceuticals production planning system using constraint programming (CP). To achieve requirements such as the shortest possible production time in safe conditions for the production process, a dual layer control system was proposed that consists of (i) a system scheduler and (ii) decentralized supervisory control and data acquisition. According to [26], the operation of chemical processes with catalysts that decay in performance over time gives rise to a challenging modeling and optimization problem.

Table 1 compares the main models [2, 25, 27] that are relevant to our proposal. The comparison includes the scope, decision variables, constraints, objective function, solution methods, and implementation. The solution method is defined by the formulation approach, solution algorithm, and solution algorithm type, and better properties are marked in bold. Lee et al. [2] were the first to present a scheduling problem and solution model for the medical cyclotron that includes transportation to hospitals. In their model, the number of batches in each cyclotron are predetermined. The solution method is a linear and discrete heuristic (large neighborhood search), and they report solving large-sized real problems. Silisteanu et al. [25] solved a total time minimization scheduling model for number and batch size via a CP optimization. They solved small-sized real problems. Akrotirianakis and Chakraborty [27] presented a scheduling and solution cost minimization model for variable cyclotron batches and transportation to hospitals. Their solution relies on the FICO-Xpress optimization package, and they managed to solve medium-sized real problems. Finally, our proposed model is based on a hybrid solution scheme that integrates analytic and random search for the relaxed model’s NLP solutions and is composed of customized construction heuristics for planning and synchronizing the SC stages. The proposed hybrid approach will prevent the dimensionality difficulties of the existing discrete optimization models. Hence, it will allow us to efficiently solve large SCs while inherently providing close to optimal alternative solutions.

Existing models for the production and distribution of decaying products consider general decaying products and specific radiopharmaceutical products. The generic models for scheduling RCs in the literature do not address the major characteristics of an RC. Existing RC models are either too computationally complex, provide a solution for part of the system, do not address the distance from optimality, do not provide alternative solutions for the decision maker, or do not consider some constraints. The proposed model and solution scheme are based on a hybrid approach that builds on the optimization advantage of a non-linear relaxed model with the efficiency advantages of search and construction heuristics.

**Table 1**. Comparison of scope, decision variables, constraints, and objective function

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Group** | **Model**  **Characteristics** | Lee et al. [2] | Silisteanu et al. [25] | Akrotirianakis & Chakraborty [27] | Our proposal |
| Scope | # of cyclotrons | up to 2 | 1 | up to 2 | **multiple** |
| # of batches (runs) | fixed | variable | variable | variable |
| # of products | 1 | **multiple** | 1 | **multiple** |
| Uncertainties addressed | no | **yes** | no | **yes** |
| Vehicle delivery | **yes** | no | **yes** | **yes** |
| Decision variables | Link demand to prod. | discrete (0/1) of injection to batch | | | **continues** |
| Production batches | used batches | # of batches | timing of batch | **# & timing** |
| Constraints | Satisfying demand | yes | yes | yes | yes |
| Limited prod. duration |  |  |  | **yes** |
| Vehicle capacity | **yes** |  | **yes** | **yes** |
| Objective function | Minimization | costs: prod., holding & delivery | duration: production | costs: prod., holding & delivery | costs: prod., holding & delivery |
| Solution methods | Formulation | monolithic | monolithic | hierarchic | **hybrid** |
| Continuous\Discrete | discrete | discrete | discrete | **continuous & discrete** |
| Linear\Non-linear | linear | non-linear | non-linear | non-linear |
| Formulation method | MIP | IP | MINLP | **NLP** |
| Solution algorithm | heuristic | optimal | optimal | **hybrid** |
| Tool | C++ language | CP-based Ilog OPL | Fico-Xpress package | R language |
| Solution algorithm type | large neighbor. search | CP |  | **analytic, random & heuristics** |
| Implementation  issues | Solves real problems | **yes** | no | **yes** | **yes** |
| Problem size | **large** | small | medium | **large** |
| Applicable | **yes** | no | **yes** | **yes** |
| Comments | | solves both production & delivery | solves the production problem | solves both production & delivery | solves both production & delivery |

1. **Research objectives and expected significance**

Objective 1: Basic model formulation, analysis, and development of an efficient solution scheme for RC systems as a specific example of an SC with decaying products.

Objective 2: Extension of the study and the RC solution scheme for various types of SC complexities and uncertainties.

Objective 3: Validation of the models and the solutions through field studies and prior knowledge of SC decision-makers.

Objective 4: To provide the basic knowledge needed for applicable modeling and solution schemes for more general SC cases with decaying or deteriorating products.

1. **Detailed description of the proposed research**
   1. **Working hypotheses**

The deterioration property of most products is addressed in practice by various efforts to reduce their life span between production and consumption. Hence, because of the complexity of SC systems, most SC model developers neglect the product deterioration property.

We argue that a hybrid approach that combines NLP relaxed modeling with existing algorithms and customized heuristics will pave the way for considering product deterioration in various types of SC models and consequently will significantly improve decision-making.

The proposed research will enable a long-term endeavor for gradually developing the basic knowledge needed for practical and applicable solutions of various types of SC while considering decaying or deteriorating products.

* 1. **Research design and methods**

Our long-term vision is to develop a new paradigm for solving the class of SC systems with decaying products. As a first major step, we focus this study on RCs as a typical and important case of such systems. The following research plan (Table 2) aims to extend the models and deepen their analysis to address the various complexities of RC SC systems. We plan to test and validate our approach both via simulation and through field experimentation in an existing RC. Finally, we plan to employ our findings to constructively review how to extend existing SC models for decaying and deteriorating products.

The first year of our research plan focuses on developing the basic model (presented in this document). This stage deals with the fundamental complexities of the RC SC, from module cell synthesis to vial dispenser planning and vehicle delivery scheduling. In principle, we should deal with several steps of lot-splitting and lot-packing together with the assignment and scheduling of these lots to meet the hospital’s injection plan in terms of time and quantity.

The second year is mostly devoted to extending the development and analysis of the relaxed model and the hybrid solution scheme for a wider class of scenarios, including multiple cyclotrons, hospitals, injection periods in each hospital, and types of radiopharmaceutical products. Each of these extensions is challenging and will require a gradual research approach with a tracking simulation study.

The third year and first half of the fourth year will consider various types of uncertainties, including production disruptions, deteriorating production yield, logistical disruptions, and injection plan changes. We plan to deal with these uncertainties in a gradual manner. Initially, we will learn their characteristics in practice via a field study and then develop risk evaluation indicators for a given solution. Next, we will modify the solution scheme to consider these risk indicators. Finally, we will develop recovery logic for dealing with such disruptions in real-time.

The last stage of the research, which will occur during the third and fourth years, will include experimenting with the model and solution scheme at an industrial site that will serve as our laboratory. The lessons learned from this experimentation will be used to improve the model and solution scheme. Finally, we will review the literature on existing SC models to explore ways in which our findings can be used to modify these models so that they can consider decaying or deteriorating products.

**Table 2.** Time schedule



* 1. **Preliminary results**

The research results achieved so far deal with the basic case of a single cyclotron that supplies the needs of a single hospital with a single demand. We first present the principles and formulation of the relaxed model. Next, we rationalize the constraints and prove the convexity of the objective function. Then, we investigate the symmetric solutions of the relaxed model. Finally, we present a solution scheme for the basic case and demonstrate it with a couple of examples.

* + 1. **Modeling**

This section outlines and formulates the relaxed model.

**RC process**

The main production and delivery stages (Figure 1) of the F-18 radiopharmaceutical are as follows: (1) raw materials are irradiated in the cyclotron to produce a batch of F-18 radioisotope; (2) the batch is fed to one of the synthesis modules for chemical reactions, producing the radiopharmaceutical product; (3) the product is portioned in a robotized dispenser module, while samples are sent for tests; (4) the bottles are delivered to the hospitals; and (5) the hospital extracts and injects the proper dose at the treatment time of each patient.



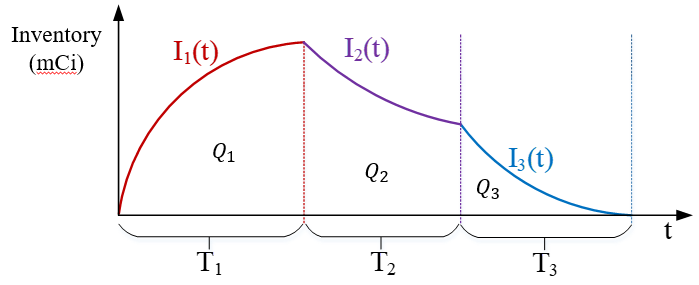
**Figure 1**. Production processes

The input data consists of the hospital’s treatment plan specifying the timing and dose for each patient (mCi). The solution output must contain data regarding each batch (Figure 2), including the batch number, production quantity (mCi), cyclotron start time, cyclotron production duration (), delay start time, delay duration (), injection start time, and injection duration ().



**Figure 2**. Solution output

The levels of inventory () in millicuries (mCi) in each of the above three main process steps are presented in Figure 3. The corresponding accumulated inventory–time functions () will enable the inventory holding cost of each batch to be expressed during the process from the start of production until the end of injection. Figure 3 demonstrates how the decay reduces the accumulation rate within production and reduces the quantity during delay, leading to a faster decline in both consumption and decay during injection.



**Figure 3**. Inventory of a single batch over time in the main three process steps

**Assumptions and notations**

Main assumptions of the basic relaxed model:

* + A single cyclotron producing one type of pharmaceutical;
  + A single hospital with a single injection period;
  + One day planning horizon (24 hours);
  + The product is continuous and decays exponentially at a constant rate ();
  + The objective function is to minimize the total cost per unit injected.

Decision variables:

* + : the integer number of batches produced to supply the daily demand;
    - : the portion of the daily demand supplied by batch (), where .

Production:

* + A constant and known production rate (), which accounts for the production yield;
  + The daily production setup spans (hours) and costs ($);
  + The batch production setup spans (hours) and costs ($);
  + : the cyclotron production duration function of batch ;
  + : the total production duration (in hours);
  + Production cost ( $/mCi).

Inventory:

* + The logistics duration () of each batch , is assumed to be a constant and mostly independent of batch size;
  + The inventory holding cost is ($/(mCihour)), which persists from start of production until the end of injection.

Demand:

* + A single demand period ();
  + A constant and known demand rate (), where the daily demand is ;
  + Injection plan duration () of batch .

Constraints:

* + Shortages are not allowed during the injection period (i.e., supply must be continuous);
  + Maximum allowed daily production duration including setup ();
  + Maximum allowed overlap () between logistic periods of consecutive batches.

**Formulation**

Minimize

**S.T.**

, portion of daily demand assigned to each batch;

, batch production durations;

, supply continuity (Proposition 1);

, daily production duration (Proposition 2);

logistic overlap (Proposition 3);

*;* and is an integer.

The objective function accounts for the main cost and loss components ($ per ordered mCi), which depend on the decision variables ( and ). Hence, daily production setup cost () is omitted, whereas per-batch setup costs () are included in the objective function.

The objective component’s expressions are defined as follows:

.

Here, is the inventory holding cost and is the production cost of batch , where

where

,

The first constraint () guarantees that the portions of the daily demand assigned to each batch satisfy the total demand. The second constraint asserts that the duration of batch production is positive. The third guarantees a continuous supply of the demand (injection plan) between consecutive batches. The fourth constraint maintains the maximum allowed daily production duration (). The fifth maintains the maximum allowed overlap () between logistic periods of consecutive batches.

* + 1. **Analysis**

This section rationalizes the duration constraints, asserts the convexity of the objective function, and discusses symmetric solutions. The main purpose of the analysis of problem **P** is to reveal important insights and provide the building blocks for the solution scheme. Because of the limited space, detailed proofs are omitted, but for some propositions, the idea of the proof is explained.

**Duration constraints**

* Supply continuity

The daily supply of batches to the hospital must ensure continuity of the injection plan.

**Proposition 1**. The condition that assures supply continuity between two consecutive batches and () is .

This means that the setup plus production durations of batch must not exceed the supply duration of batch . This is a useful and intuitive insight, but is not trivial. The explicit form of this condition on is

* Limited daily production period

The total daily production duration, including setup, is limited by .

**Proposition 2**. The condition that maintains the daily production duration limit is

This means that enlarging reduces the daily production duration, a useful insight that is somewhat counterintuitive (see the numerical example).

* Maximal allowed logistic overlap

The logistic periods of consecutive batches (and) utilize limited facilities (for the synthesis, vial-dispensing, and delivery steps). The allowed portion of logistic overlap is , where 0 means no overlap and 1 means a full overlap, is permitted. This means that the logistic period of batch can overlap by up to of the logistic period of batch .

**Proposition 3**. The allowed overlap between the logistic periods of consecutive batches limits as follows: .

This condition means that the non-overlapped duration () between the logistic delays of batch and batch should not exceed the supply duration of batch . Any violation of this condition would harm the supply continuity.

The set of constraints determines the feasible solution space, which is split by the number of batches and determines the dimension of . The analysis and the solution scheme rely on this observation.

**Objective convexity**

**Proposition 4**. The objective function of **P** for a given is a convex function of .

The proof verifies (by studying the first and second derivatives) that each of the functions is convex w.r.t. , and hence and (and thus ), are convex functions w.r.t. . Finally, since is a sum of separable convex functions, each in one component of , is convex in **.**

**Definition 1.** A solution for a given is called *symmetric* if

**Proposition 5**. If, for a given , a symmetric solution of **P** is feasible, then it is the best solution of **P** for that .

Hence, for any specific problem instance, feasible symmetric solutions seem attractive but are not always feasible for a given . Thus, it is worth exploring symmetric solutions, but we cannot ignore non-symmetric ones. Nonetheless, in the search for feasible non-symmetric solutions for a given , the symmetric solution may provide a useful lower bound for Z and a guide for the search for feasible solutions. For further analysis of symmetric solutions, we define the following problem.

**Symmetric solutions**

By imposing in problem ,we obtain an equivalent problem for deriving a symmetric solution through functions of as follows.

Minimize

**S.T.**

, production duration of a single batch;

, supply continuity (Proposition 1);

, production period (Proposition 2);

delay overlap (Proposition 3);

and is an integer*.*

Here, for a symmetric solution.

In principle, among the symmetric solutions, it is worth asking which minimizes Z. Let us consider it while ignoring the duration constraints and the integrality constraint of .

**Proposition 6**. The objective function of **PK** is a convex function in .

The proof derives the first and second derivatives of the components of and then derives those of .

Following Proposition 3, it is worth asking which continuous minimizes **PK**. We could not find a closed-form expression for , but a Newton–Rapson search can rapidly determine this value. Once has been identified, the neighboring integer can be used to evaluate and verify feasibility. Some solutions might be feasible, in which case, we have a candidate solution for that . Moreover, some might be infeasible but useful for searching for feasible non-symmetric solutions of for that .

**Proposition 7**. The feasible values of for solving **PK** satisfy the following conditions: , , , , and if , then .

The proof is straightforward by isolating in each constraint of **PK**. Thus, the constraints of determine the closed-form lower and upper bounds for with feasible symmetric solutions.

* + 1. **Solution procedure**

Outline of the solution scheme

Figure 4 presents the main solution scheme that solves the relaxed model and that iteratively calls a procedure for the construction of a detailed implementable solution, as presented in Figure 5. The main solution scheme returns a list sorted in increasing order of alternative feasible solutions with the best objective values found. The decision-maker can then choose the final solution from . The scheme is composed of three main components, as follows.

Main procedure

This procedure begins with ***Settings Initialization***. Next, it iterates through ObjLB(). In each iteration, is set to be the with the next lowest ObjLB(). However, we skip if , which states that no solution with that can improve the existing solutions in . For the selected , we search for feasible solutions, as described in the ***Construct solutions for kʹ*** component (Figure 5).

Settings initialization

This component sets the required problem parameters and calculates the preliminary lower and upper bounds for the number of batches (), as identified by Propositions 3 and 7. Next, for each within the bounds, we calculate the objective function of a symmetric solution (ObjLB() for identical ’s). (Note that in large problems, we should limit the search of solutions neighboring *k*\* as proposed in Section 3.3.2. Since we have a small number of integer options between and , we iterated through all options.) Although the symmetric solution is not necessarily feasible, ObjLB() is a lower bound for any feasible solution of batches (based on Proposition 5). List is initialized with large numbers .

|  |  |
| --- | --- |
|  |  |

**Figure 4**. Flow chart of the main solution scheme

Construct solutions for (a given)

This component randomly draws vectors of size each. The first sample created is the symmetric (i.e., ). The rest of the samples are drawn from a uniform distribution bounded by a lower bound () and an adjusted upper bound corrected for each batch (to ensure a sum of 1 and ). To generate a diversity of solutions, we use a dissimilarity metric to ensure that any new is not too close to any of the previously sampled for the same . Each sampled is examined by a sequence of tests. First, we check feasibility (Propositions 1–3). Second, for a feasible , we construct a discrete treatment schedule and test whether it remains feasible. Finally, if then replaces , which is the worst solution accumulated so far in (while keeping the ascending order of **)**. The procedure repeats until we reach feasible instances of (for each ).

|  |  |
| --- | --- |
|  |  |

**Figure 5.** ***Construct solutions for***  procedure

* + 1. **Numerical demonstration**

This section demonstrates the solution scheme for a given scenario of production and demand settings. This example highlights the effect of the different constraints and how a feasible solution is reached. For simplicity, we demonstrate a non-feasible symmetric solution and one specific non-symmetric sample of ***w*** that fulfills the constraints. The example follows the main procedure components shown in Figures 4 and 5.

**Settings initialization:**

***Obtain the data:***

Orders

,, First Injection Time , Time Between Injections

Production

Constraints

***Calculate the bounds:***

***Calculate the* PK *objective:***

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **2** | **3** | **4** | **5** | **6** | **7** |
|  | 52.27 | 19.79 | 15.15 | 13.9 | **13.74** | 14.07 |

Initially, was set to 6 with the minimal ObjLB value. Applying the ***Construct solutions for kʹ*** procedure did not yield a feasible solution: for the symmetric (solution #1: ), the production cycle time () exceeds the constraint (); therefore, it is not a feasible solution. No other non-symmetric solution was found.

The next value of ***kʹ*** was 5 (the next minimal ObjLB value). For the symmetric (solution #2: ), the production cycle time exceeds the constraint (); therefore, it is again not a feasible solution. In this case, the ***Construct solutions for kʹ*** procedure found non-symmetric feasible solutions. For demonstration purposes, we consider one of the solutions (solution #3: ), which has an objective function value of 17.91 and production cycle ; therefore, it is feasible. Table 3 shows the detailed solution generated for the relaxed problem, which includes batch start and end times for production, delay, and treatment. Although the total quantity produced meets the total demand, the relaxed solution’s weights need to be corrected to meet the discrete treatment plan, as shown in Table 4. For example, the delivered quantities of the first and third batches are less than required and in the second, fourth, and fifth batches, the delivered quantities are greater than required. Table 5 and Figure 6 present the detailed times and Gantt chart derived for the corrected solution #3 with an objective function value of 17.86.

**Table 3.** Weights and time data (hours from the initial time 0) of the relaxed model, solution #3.

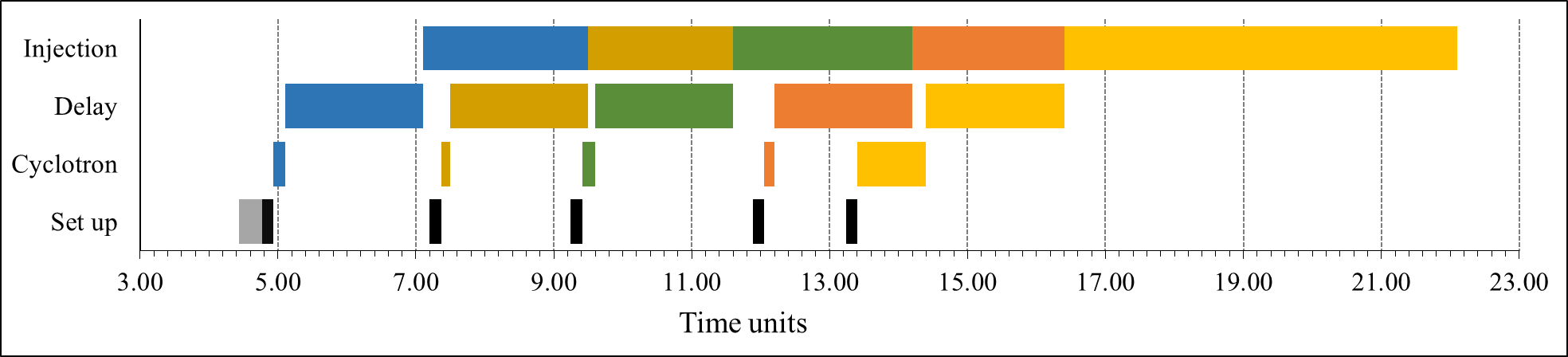
|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Batch index | Batch portion | Production period | | Delay period | | Injection period | |
| () |  | Start  time | Finish time | Start time | Finish time | Start time | Finish time |
| 1 | 0.154 | 4.94 | 5.10 | 5.10 | 7.10 | 7.10 | 9.41 |
| 2 | 0.143 | 7.27 | 7.41 | 7.41 | 9.41 | 9.41 | 11.56 |
| 3 | 0.171 | 9.37 | 9.56 | 9.56 | 11.56 | 11.56 | 14.12 |
| 4 | 0.151 | 11.97 | 12.12 | 12.12 | 14.12 | 14.12 | 16.39 |
| 5 | 0.381 | 13.38 | 14.39 | 14.39 | 16.39 | 16.39 | 22.10 |

**Table 4**. Corrected weights for solution #3 obtained using the discretization process.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Relaxed solution | | Corrected discrete solution | |
| Batch index () | Batch  relative size | Treatment  quantity (mCi) | Treatment  quantity (mCi) | Batch  relative size |
| 1 | 0.154 | 221.76 | 230.4 | 0.160 |
| 2 | 0.143 | 205.92 | 201.6 | 0.140 |
| 3 | 0.171 | 246.24 | 249.6 | 0.173 |
| 4 | 0.151 | 217.44 | 211.2 | 0.147 |
| 5 | 0.381 | 548.64 | 547.2 | 0.380 |
| Total (mCi) |  | 1,440 | 1,440 |  |

**Table 5**. Weights and time data (hours from the initial time 0) of the corrected solution #3.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Batch index | Batch portion | Production period | | Delay period | | Injection period | |
| () |  | Start time | Finish time | Start time | Finish time | Start time | Finish time |
| 1 | 0.160 | 4.93 | 5.10 | 5.10 | 7.10 | 7.10 | 9.50 |
| 2 | 0.140 | 7.37 | 7.50 | 7.50 | 9.50 | 9.50 | 11.60 |
| 3 | 0.173 | 9.41 | 9.60 | 9.60 | 11.60 | 11.60 | 14.20 |
| 4 | 0.147 | 12.06 | 12.20 | 12.20 | 14.20 | 14.20 | 16.40 |
| 5 | 0.380 | 13.40 | 14.40 | 14.40 | 16.40 | 16.40 | 22.10 |



**Figure 6.** Corrected solution #3: ; thus, it is a feasible solution.

Table 6 summarizes the sensitivity of the solutions to the constraints. For the shortage and overlap constraints, we calculated the minimal, maximal, and average slack. For the cycle time constraint, we calculated the additional time between the constraint and production time. All solutions meet the shortage and overlap constraints, but solutions #1 and #2 exceed the production duration limit () by 2.68 h and 2.24 h, respectively.

The data in Table 6 can support operational decisions. For example, we can determine how much downtime we can schedule for maintenance without affecting the treatment schedule. Table 6 reveals that the minimal slack for the shortage constraint is 1.2 h, suggesting that this is the maximum time allowed for planned downtime. We can also see that the delivery interruption is limited to 0.1 h before it affects the treatment schedule.

**Table 6.** Summary of solution sensitivity to the constraints

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Solution #** | | | | | | | | | | | |
| **Constraint** | **1** | | | **2** | | | **3** | | | **3 corrected** | | |
| ***Supply continuity:*** () | Avg. | Min. | Max. | Avg. | Min. | Max. | Avg. | Min. | Max. | Avg. | Min. | Max. |
| 2.32 | 2.32 | 2.32 | 2.76 | 2.76 | 2.76 | 1.95 | 1.26 | 2.41 | 1.96 | 1.2 | 2.46 |
| ***Production cycle:*** | 2.68 | | | 2.24 | | | −0.56 | | | −0.53 | | |
| ***Overlap:*** () | Avg. | Min. | Max. | Avg. | Min. | Max. | Avg. | Min. | Max. | Avg. | Min. | Max. |
| 0.50 | 0.50 | 0.50 | 1.00 | 1.00 | 1.00 | 0.32 | 0.15 | 0.57 | 0.32 | 0.1 | 0.6 |

* 1. **Research conditions**

The research team comprises members with practical and theoretical expertise in operations research, production management, industrial control, decision support systems, and scheduling. They offer a wide research experience with various relevant research methodologies such as non-linear optimization modeling and analysis, customized optimization algorithm development, simulation model development, experiment design and analysis, decision support system development, and the design and implementation of organizational performance indicators. We also plan to recruit a few research students for our important and interesting endeavor.

During the first three years, while we mostly develop analyze, and test models, we will need a strong computation machine and laptops for the PI and students. To validate the models in practice, during the last two years, we will need an industrial computer programmer and means of collaboration with practical RC systems. We already collaborate with the cyclotron facility at the Hadassah University Medical Center.

* 1. **Expected results and potential pitfalls**

We expect to achieve the following major results:

* A basic model solution for one cyclotron and one demand source. The model will include lot scheduling for synthesis and vial dispensing as well as delivery planning for varying demand rates.
* An extended model and solution for more complex cases with multiple cyclotrons, hospitals, and demand periods.
* We will incorporate risks and uncertainty aspects into the extended model. These will include operational logic for disruption recovery as the basis for future decision support systems.
* A thorough review of the SC literature to propose ways of considering decaying or deteriorating products.

Potential pitfalls are as follows:

* The need to decide upon a solution approach from a possible set of strategies may lead to a “dead end” at the modeling stage. To reduce the damage of such a pitfall, the research plan includes frequent simulation studies.

1. **References**

|  |  |
| --- | --- |
| [1] | D. A. Rich, "A brief history of positron emission tomography," *Journal of nuclear medicine technology,* vol. 25, no. 1, pp. 4-11, 1997. |
| [2] | J. Lee, B. I. Kim, A. L. Johnson and K. Lee, "The nuclear medicine production and delivery problem," *European Journal of Operational Research,* vol. 236, no. 2, pp. 461-472, 2014. |
| [3] | S. Panda, S. Senapati and M. Basu, "Optimal replenishment policy for perishable seasonal products in a season with ramp-type time dependent demand," *Computers & industrial engineering,* vol. 54, no. 2, pp. 301-314, 2008. |
| [4] | C. T. Chang, L. Y. Ouyang and J. T. Teng, "An EOQ model for deteriorating items under supplier credits linked to ordering quantity," *Applied Mathematical Modelling,* vol. 27, no. 12, pp. 983-996, 2003. |
| [5] | G. A. Widyadana and H. M. Wee, "Optimal deteriorating items production inventory models with random machine breakdown and stochastic repair time," *Applied Mathematical Modelling,* vol. 35, no. 7, pp. 3495-3508, 2011. |
| [6] | F. W. Harris, "How Many Parts to Make at Once," *Factory, The Magazine of Management, 10(2), 135-136, 152. Reprinted in Operations Research, 1990, 38(6), 947-950,* 1913. |
| [7] | R. H. Wilson, "A scientific routine for stock control," *Harvard University,* 1934. |
| [8] | N. Mahapatra and M. Maiti, "Decision process for multiobjective, multi-item production-inventory system via interactive fuzzy satisficing technique," *Computers & Mathematics with Applications,* vol. 49, no. (5-6), pp. 805-821, 2005. |
| [9] | Z. T. Balkhi, "The effects of learning on the optimal production lot size for deteriorating and partially backordered items with time varying demand and deterioration rates," *Applied Mathematical Modelling,* vol. 27, no. 10, pp. 763-779, 2003. |
| [10] | A. Roy, M. K. Maiti, S. Kar and M. Maiti, "An inventory model for a deteriorating item with displayed stock dependent demand under fuzzy inflation and time discounting over a random planning horizon," *Applied Mathematical Modelling,* vol. 33, no. 2, pp. 744-759, 2009. |
| [11] | P. M. Ghare, "A model for an exponentially decaying inventory," *J. ind. Engng,* vol. 14, pp. 238-243, 1963. |
| [12] | H. Emmons, "A replenishment model for radioactive nuclide generators," *Management Science,* vol. 14, 1968. |
| [13] | R. P. Covert and G. C. Philip, "An EOQ model for items with Weibull distribution deterioration," *AIIE transactions,* vol. 5, no. 4, pp. 323-326, 1973. |
| [14] | G. C. Philip, "A generalized EOQ model for items with Weibull distribution deterioration," *AIIE transactions,* vol. 6, no. 2, pp. 159-162, 1974. |
| [15] | R. B. Misra, "Optimum Production lot-size model for a system with deteriorating inventory," *International Journal of Production Research,* vol. 13, pp. 495-505, 1975. |
| [16] | P. R. Tadikamalla, "An EOQ inventory model for items with gamma distributed deterioration," *AIIE transactions,* vol. 10, no. 1, pp. 100-103, 1978. |
| [17] | A. Bhunia and A. Shaikh, "A deterministic inventory model for deteriorating items with selling price dependent demand and three-parameter Weibull distributed deterioration," *International Journal of Industrial Engineering Computations,* vol. 5, no. 3, pp. 497-510, 2014. |
| [18] | E. W. Taft, *The most economical production lot. Iron Age,* vol. 101, no. 18, pp. 1410-1412, 1918. |
| [19] | K. S. Park, "An integrated production-inventory model for decaying raw materials. International Journal of Systems Science," vol. 14, no. 7, pp. 801-806, 1983. |
| [20] | Z. T. Balkhi and L. Benkherouf, "A production lot size inventory model for deteriorating items and arbitrary production and demand rates," *European Journal of Operational Research,* vol. 92, no. 2, pp. 302-309, 1996. |
| [21] | P. C. Yang and H. M. Wee, "An integrated multi-lot-size production inventory model for deteriorating item," *Computers & Operations Research,* vol. 30, no. 5, pp. 671-682, 2003. |
| [22] | T. Kim, C. H. Glock and Y. Kwon, "A closed-loop supply chain for deteriorating products under stochastic container return times," *Omega‏,* vol. 43, pp. 30-40, 2014. |
| [23] | C. K. Chan, W. H. Wong, A. Langevin and Y. C. E. Lee, "An integrated production-inventory model for deteriorating items with consideration of optimal production rate and deterioration during delivery," *International Journal of Production Economics,* vol. 189, pp. ‏1-13, 2017. |
| [24] | T. Borangiu, S. Răileanu, V. E. Oltean and A. Silişteanu, "Holonic Hybrid Supervised Control of a Radiopharmaceutical Production Plant," *IFAC-PapersOnLine,* vol. 51, no. 11, pp. 1249-1254, 2018. |
| [25] | A. Silisteanu, T. Borangiu, S. Raileanu and E. V. Oltean, "Optimized Planning of radiopharmaceutical Production in Holonic Control Framework," *University Politehnica of Bucharest Scientific Bulletin Series C-Electrical Engineering and Computer Science,* vol. 79, no. 3, pp. 3-18, 2017. |
| [26] | V. M. Bizet, I. E. Grossmann and N. M. Juhasz, "Optimal production and scheduling of a process with decaying catalyst," *AIChE journal,* vol. 51, no. 3, pp. 909-921, 2005. |
| [27] | I. Akrotirianakis and A. Chakraborty, "A multi-period production and distribution optimization model for radiopharmaceuticals," in *10th International Conference on MOdeling, Optimization and SIMlation - MOSIM16, “Innovation in Technology for Performant Systems: Challenges and Opportunities”*, Montreal - Canada, 2016. |
| [28] | C. T. Chang, L. Y. Ouyang, J. T. Teng and M. C. Cheng, "Optimal ordering policies for deteriorating items using a discounted cash-flow analysis when a trade credit is linked to order quantity," *Computers & Industrial Engineering,* vol. 59, no. 4, pp. 770-777, 2010. |
| [29] | "Cyclotron produced radionuclides: guidelines for setting up a facility," Vienna, 2009. |
| [30] | C. H. Kim and Y. Hong, "An optimal production length in deteriorating production processes," *International journal of Production Economics,* vol. 58, p. 183–189, 1999. |
| [31] | K. S. PARK, "An integrated production-inventory model for decaying raw materials," *International Journal of Systems Science,* vol. 14, no. 7, pp. 801-806, 1983. |
| [32] | H. M. Wagner and T. M. Whitin, "Dynamic version of the economic lot size model," *Management science,* vol. 5, no. 1, pp. 89-96, 1958. |
| [33] | P. C. Yang and H. M. Wee, "An integrated multi-lot-size production inventory model for deteriorating item," *Computers & Operations Research,* vol. 30, no. 5, pp. 671-682, 2003. |
| [34] | M. Namakshenas, M. Mazdeh, A. Braaksma and M. Heydari, "Appointment scheduling for medical diagnostic centers considering time-sensitive pharmaceuticals: A dynamic robust optimization approach," *European journal of operational research,* vol. 305, no. 3, pp. 1018-1031, 2023. |
| [35] | C. T. Chang, L. Y. Ouyang, J. T. Teng and M. C. Cheng, "Optimal ordering policies for deteriorating items using a discounted cash-flow analysis when a trade credit is linked to order quantity," *Computers & Industrial Engineering,* vol. 59, no. 4, pp. 770-777, 2010. |