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 decaying products. Radiopharmaceutical cyclotrons (RC) are small supply chain (SC) systems with several cyclotrons serving a network of customer hospitals. From learning the literature, we encountered lack of SC planning and scheduling models for decaying (or deteriorating) products. We did find a few restricted models for RC systems. In this work we intend to address this fundamental gap. Since SC is a very broad types of systems, one must focus such research endeavor on a specific type. Hence we chose to focus our research efforts on the case of RC, being a small SC with rapidly decaying product.

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

In 1913, Ford W. Harris [6] developed the economic order quantity (EOQ) formula whereas Wilson is given credit for the application and in-depth analysis of this model [7]. According to the existing literature of inventory control system, it is normally assumed that the lifetime of an item is infinite [8]. While in real life situations, this assumption is a reasonable approximation, in various scenarios it is not. Several researchers focus their study on deteriorating items [9, 10, 4]. Ghare [11] has 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, by a two-parameter Weibull distribution. Misra [15] developed an EOQ model with 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 items.

Taft [18] was the first to develop the economic production quantity (EPQ) model. [19] presented an EPQ model that included exponentially deteriorating raw materials with a non-deteriorating product. Balkhi and Benkherouf [20] presented a production lot size inventory model for exponentially deteriorating items, where the demand and the 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 a supply chain using returnable transport items (RTIs) for shipments. Chan et al. [23] presented an integrated production-inventory model for exponentially deteriorating items, assuming constant demand and production rates, shortages are not allowed and immediate shipments.

The production of radiopharmaceuticals is in the class of semi-continuous manufacturing processes characterized by continuous flows which 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. The hybrid control comprises a discrete event part for the supervisory control which 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 shortest possible production time in safety conditions for the production process, a dual layer control system is proposed: (i) system scheduler) and (ii) decentralized Supervisory Control and Data Acquisition. According to [26] the operation of chemical processes with catalysts having decaying performance over time gives rise to a challenging modeling and optimization problem.

Tables 1 compares the main relevant models we found [2, 25, 27] versus our proposal. The comparison presents scope, decision variables, constraints, objective function, solution methods, and implementation. The solution method is defined by the formulation approach, solution algorithm and the solution algorithm type. The better properties are marked bold. Lee et al. [2] were the first to present a scheduling problem and solution model for the medical cyclotron including transportation to hospitals. In their model, the number of batches in each cyclotron were predetermined. The solution method was linear and discreet heuristic (large neighborhood search). They report solving large size real problems. Silisteanu et al. [25] solved a total time minimization scheduling model for number and size of batches, via a constraint programming optimization. They solved small size real problems. Akrotirianakis and Chakraborty [27] present a scheduling and solution cost minimization model for variable cyclotron batches and transportation to hospitals. Their solution relied on FICO-Xpress optimization package. They managed to solve medium-sized real problems. Finally, our proposed model is based on a hybrid solution scheme, integrating analytic and random search for the relaxed model’s NLP solutions, composed with 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 allows us to efficiently solve large size of SCs while inherently providing close to optimal alternative solutions.

Existing models for production and distribution of decaying products consider general decaying products and specific radiopharmaceutical products. The generic models for scheduling RC in the literature do not address major characteristics of the RC characteristics. Existing RC models are either too complex computationally, provide solution for part of the system, do not address distance from optimality, do not provide alternative solutions for the decision maker, or do not consider some of the constraints. The proposed model and solution scheme is based on a hybrid approach which builds on the optimization advantage of a non-linear relaxed model with 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** |
| Vehicles 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 | discreet | discreet | discreet | **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 (LNS) | constraint programming |  | **analytic, random & heuristics** |
| Implement  issues | Solves real problems | **yes** | no | **yes** | **yes** |
| Problem size | **large** | small | medium | **large** |
| Applicable | **yes** | no | **yes** | **yes** |
| Comments | | solving both production & delivery | solves the production problem | solving both production & delivery | solving 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 SC with decaying products.

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

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

Objective 4: 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 for squeezing their life span from production till consumption. Hence, due to the complexity of SC systems, most SC model developers neglect the product deterioration property.

We advocate that a hybrid approach which 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 opens 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 deterioration products.

* 1. **Research design and methods**

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

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

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 multiples of cyclotrons, hospitals, injection periods in a hospital, and types of radiopharmaceutical products. Each of these extensions is challenging and will require a gradual research approach with tracking simulation study.

The third and half of the fourth years will cope with 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 by learning their behavior in practice via a field study, then by developing risk evaluation indicators for a given solution. Next, by modifying the solution scheme to consider these risk indicators. Finally, by developing a recovery logic for dealing in real time with such disruptions.

The last stage of the research, during the third and the fourth years, will include experimenting with the model and solution scheme at an industrial site that will serve as our lab. The lessons learned from this experimentation will be used for improving the model and the solution scheme. Finally, we will review the literature of existing SC models for exploring ways by which our findings can be used for modifying these models for considering decaying or deteriorating products.

**Table 2.** Time Schedule



* 1. **Preliminary results**

The research results so far deal with the basic case of a single cyclotron that supplies the need of a single hospital with a single demand. We present relaxed model principles and formulation. 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.

**The RC process**

The main production and delivery stages (Figure 1) of the F-18 radiopharmaceutical are: (1) raw materials are irradiated in the cyclotron to produce a batch of the 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 one of the robotized dispenser modules, while samples are sent to 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.



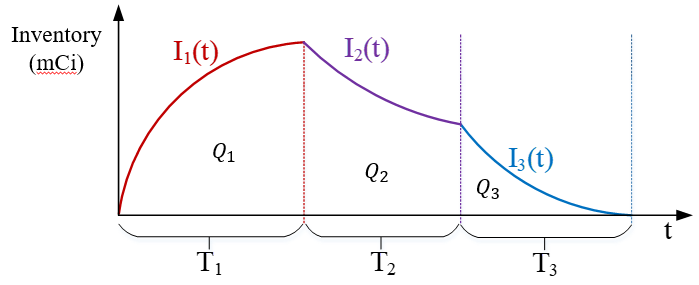
**Figure 1** – The production processes

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



**Figure 2** - The solution output

The amount of millicuries inventory levels () (in each of the above three main process steps) are presented schematically in Figure 3. The corresponding accumulated inventory-time () functions, will enable expressing the inventory holding cost of each batch, along the process, from start of production till end of injection. Figure 3 demonstrates how the decay reduces the accumulation rate within production, reduces the quantity during delay, and the faster decline by both consumption and decay during injection.



**Figure 3** – A single batch inventory over time, along 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 ),
  + The product is continuous and decaying exponentially with a constant rate (),
  + The objective function is to minimize the total cost per unit injected.

Decision variables

* + – the integer number of batches produced for supplying the daily demand,
    - - the portion of the daily demand supplied by batch (); .

Production

* + 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 (),
  + Production cost ( $/mCi).

Inventory

* + Logistics duration () of each batch , is assumed constant, mostly independent of batch size,
  + Inventory holding cost is ($/(mCihour)), persists from start of production till end of injection.

Demand

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

Constraints

* + Shortage not allowed during the injection period (i.e. supply continuity),
  + Maximum allowed daily production duration () including setups,
  + Maximum allowed overlap () between logistic periods of consecutive batches.

**Formulation**

Minimize

**S.T.**

, batches’ portions of the daily demand,

, batches’ production durations,

, supply continuity (Proposition 1),

, daily production duration (Proposition 2),

logistic overlap (Proposition 3),

*;* and 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, while per batch setup costs () are included in the objective function.

The objective component’s expressions are defined as follows.

Where 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 positive duration of batch production. The third guarantees continuous supply of the demand (injection plan) between each two 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. Due to the limited space, the detailed proofs are omitted, for some propositions the proof idea is explained.

**Duration constraints**

* Supply continuity

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

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

It means that the setup plus production durations of batch must not exceed the supply duration of batch . Useful insight which makes sense but not trivial. The explicit form of this condition on is:

* Limited daily production period

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

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

It means that enlarging , reduces the daily production duration, useful insight which is somewhat counter intuitive (see numerical example).

* Maximal allowed logistic over-lap

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

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

The condition means that the non-overlapped duration () between the logistic delays of batch and of 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, that 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 with , and hence and , and thus also , are convex functions with . Finally, since is a sum of separable convex functions, each in one component of , then 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 a feasible non-symmetric solutions for a given , the symmetric solution may provide useful lower bound for Z and a guide for searching feasible solutions. For further analysis of symmetric solutions, we define the following problem.

**Symmetric solutions**

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

Minimize

**S.T.**

, a single batch production duration,

, supply continuity (Proposition 1),

, production period (Proposition 2),

delay overlap (Proposition 3),

and integer*.*

Where , for symmetric solution.

In principle, among the symmetric solutions it worth asking which minimizes Z? Let’s 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 of .

Following Proposition 3 it worth asking which continues minimizes **PK**. We could not find a closed form expression for , but a Newton-Rapson search can rapidly find it. Once is identified, neighboring integer ’s can be used for evaluating and verifying feasibility. Some might be feasible then we have a candidate solution for that , and some infeasible but useful for searching 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 through isolating in each constraint of **PK**. Thus, the constraints of determines closed form lower and upper bounds for with feasible symmetric solutions.

* + 1. **Solution Procedure**

The solution scheme outline

Figure 4 presents the main solution scheme that solves the relaxed model, and which iteratively calls for the construction procedure of detailed implementable solution, presented by Figure 5. The main solution scheme returns an ascendingly sorted list of the alternative feasible solutions with the best objective values found, for the choice of the decision maker. The scheme is composed of three main components as follows.

Main procedure – The procedure begins with ***Settings Initialization***. Next, it iterates through ObjLB(). In each iteration is set to be the with the next lowest ObjLB(). But we skip if , meaning 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 k’*** component (Figure 5).

Settings Initialization -This component sets the needed 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: 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 we Iterated through all options) Although the symmetric solution is not necessarily feasible, the ObjLB() is a lower bound for any feasible solution of batches (based on Proposition 5). The list is initialized by 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 for asserting 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, 2, 3). Second, for a feasible , we construct a discrete treatment schedule and test if it retains feasible. Finally, if then replaces , 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

* + 1. **Numerical Demonstration**

This section demonstrates the solution scheme for a given scenario of production and demand settings. The 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*** which fulfils the constraints. The example follows the main procedure components shown in Figures 4 and 5.

**Settings Initialization:**

***Get data:***

Orders

,, First Injection Time , Time Between Injections

Production

Constraints

***Calculate bounds:***

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

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

Initially, is set to be 6 with minimal ObjLB value. Applying ***“Construct solutions for k’”*** did not find a feasible solution: For the symmetric (solution #1: ), the production cycle time () exceeds the constraint (), therefore not a feasible solution. No other non-symmetric solution was found.

The next ***k’*** is set to 5 (the next minimal ObjLB value). For the symmetric (solution #2: ), the production cycle time exceeds the constraint (), therefore not a feasible solution. In this case, ***“Construct solutions for k’”*** found non-symmetric feasible solutions. For demonstration purposes we chose one of the solutions (solution #3: ) with an objective function’s value of 17.91 and production cycle , therefore feasible. Table 3 shows the detailed solution generated for the relaxed problem: Batch start and end times for production, delay and treatment. Althogh the total quantity produced meets the total demand, the relaxed solution’s weights need to be corrected to meet the descrete treatment plan as shown in Table 4. For example, the first and third batches’ delivered quantities are less than required and in the second, fourth and fifth batches’ delivered quantities which are greater than required. Table 5 and Figure 6 show 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 datum 0) by the relaxed model, solution #3.

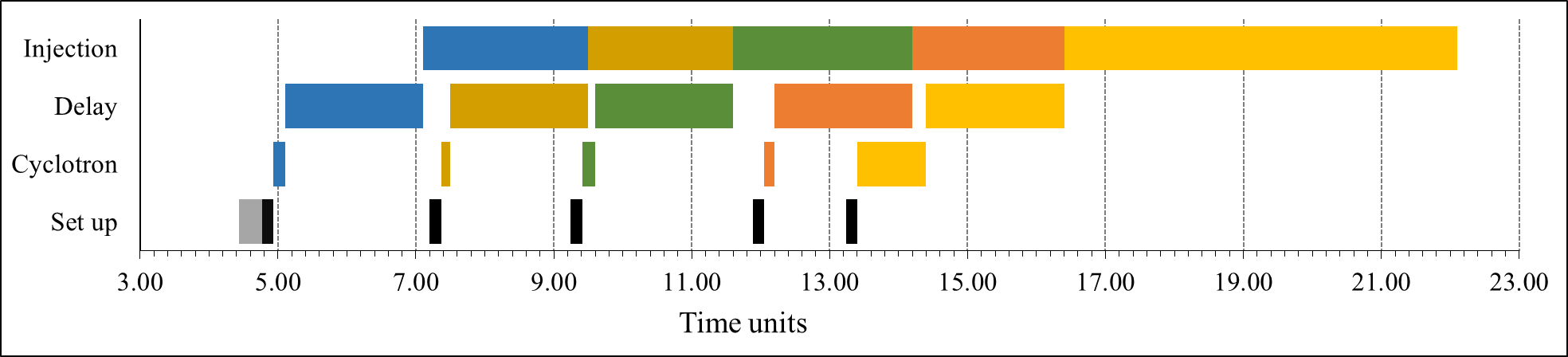
|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Batch index | Batch portion | Production period | | Delay period | | Injection period | |
| () |  | Start  time | Finish time | Start time | Finish time | Start time | Finish time |
| 1 | 0.154 | 4.94 | 5.10 | 5.10 | 7.10 | 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, by the discratization 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 datum 0) of 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 a feasible solution.

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

The data in Table 6 can support operational decisions. For examle, how long can we schedule down-time for maintanance without effecting the treatment schedule. Looking at table 6, we can see that the minimal slack for the shortage constraint is 1.2 , suggesting that this is the maximal time allowed for planned down-time. We also see the delivery interruption is limited to 0.1 before affecting the treatment schedule.

**Table 6.** Summary of solutions sensitivity to constraints

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Solution#** | | | | | | | | | | | |
| **Constraints** | **1** | | | **2** | | | **3** | | | **3 corrected** | | |
| ***Supply continuity:*** () | Av | Min | Max | Av | Min | Max | Av | Min | Max | Av | 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 |
| ***Pruduction Cycle:*** | 2.68 | | | 2.24 | | | -0.56 | | | -0.53 | | |
| ***Overlap:*** () | Av | Min | Max | Av | Min | Max | Av | Min | Max | Av | 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 practical and theoretical expertise in operations research, production management, industrial control, decision support systems, scheduling. They offer a wide research experience with various relevant research methodologies such as non-linear optimization modeling and analysis, development of customized optimization algorithms, development of simulation models, design and analysis of experiments, development of decision support systems, and design and implementation of organizational performance indicators. We plan to recruit a few research students for joining 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 the students. For validating the models in practice, during the last two years, we will need some industrial computer programmer and collaboration means 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 folowing major results:

* A basic model solution for one cyclotron and one demand source. The model will include a lot scheduling of synthesis and vial dispensing, and planning of delivery for varying demand rate.
* An extended model and solution for more complex cases with multiple cyclotrons, hospitals, demand periods.
* Incorperate risks and uncertenty aspects into the extended model. These will include operational logic for disruptions recovery as the basis for future decision support system.
* A thorough review of the SC literature for proposing ways for considering decaying or deteriorating products.

Potential pitfalls:

* The need to decide upon a solution approach from a possible set of strategies, may lead to a “dead end” at the modeling stage. For reducing the damage of such a pitfall, the reseach 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. |