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Discrete Optimization

The nuclear medicine production and delivery problem

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ABSTRACT

Half-life is a unique characteristic of radioactive substances used in a variety of medical treatments. Radioisotope F-18 used for diagnosing and monitoring many types of cancers has a half-life of 110 minutes. As such, it requires careful coordination of production and delivery by manufacturers and medical end-users. To model this critical production and delivery problem, we develop a mixed integer program and propose a variant of a large neighborhood search algorithm with various improvement algorithms. We conduct several computational experiments to demonstrate the effectiveness of the proposed approach. The method when applied in a case study shows that improvement in terms of both time and cost is possible in the production and delivery of F-18.

1. Introduction

To our knowledge, no previous work has considered the nuclear medicine production and delivery problems (NMPDP) posed by F-18, an isotope that requires scrupulous determination of manufacturing levels as well as accounting for its rapid deterioration. In this paper we develop a mixed integer programming (MIP) model and propose a variant of a large neighborhood search (LNS) algorithm with various improvement algorithms. We conduct several computational experiments to demonstrate the effectiveness of the proposed approach. We conclude that the approach will help manufacturers and the medical community produce and deliver F-18 considering both time and cost.

The remainder of this paper is organized as follows. The detailed problem is described in Section 2. A literature review is presented in Section 3. The MIP model and our proposed approach are presented in Sections 4 and 5. Our experimental results are shown in Section 6. A case study is presented in Section 7 and our concluding remarks are presented in Section 8.

2. Problem description

The description below is based on a manufacturer that produces only radioisotope F-18 that we observed. Physicians order nuclear medicine, such as F-18, based on a specified level of radiation according to their injection plans for the medicine. The manufacture gathers a set of customer orders a day in advance, each of which corresponds to a hospital and perhaps multiple patients, and schedules delivery vehicles to visit each hospital. Each customer has a requested quantity of F-18 and time window for delivery. The end of time window corresponds to the medicine's usage time. F-18's half-life, 110 minutes, is the elapsed time until the number of atoms reduces to the half of its initial state. To meet the specified radiation level, the quantity of medicine produced is determined based on the production time and the usage time accounting for F-18's half-life. The production quantity must be equal to $d_i 2^{(l_i - f_i)/HL}$, where d_i, l_i, f_i and HL correspond to demand radiation quantity, use time, production termination time of order i, and the half-life, respectively.

The F-18 manufacturer batches customer orders in a production run. The factory has multiple cyclotrons, each capable of multiple production runs in a day. In this paper, we divide a cyclotron's production capacity into production runs with fixed start and end times. Management typically schedules the cyclotrons to cope with F-18's unpredictable low yield, which results from the process's stochastic nature. For this reason the manufacturer we observed prefers preset production runs although they may cause delivery vehicles to wait or excessive use of cyclotrons. We assume that when a production run is used, a fixed production cost occurs regardless of the production quantity, and that if no customer orders are assigned to a production run, there is no production cost for the run.

In the problem, vehicles with different capacities, i.e., heterogeneous vehicles, are available for delivery from the plant to the

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customer stops. Time windows in which the vehicles are available are given and multiple trips per vehicle are allowed. Special packaging[1] protects workers and the public from radiation, and maintains product integrity. Split deliveries are not allowed and a single vehicle services a customer order.

We summarize the assumptions in the model to characterize the manufacturer's operations:

- The manufacturer has K different machines (cyclotrons) with different capacity.
- Each machine has a fixed number of scheduled production runs with fixed start and end times.
- One or many production runs can be skipped when appropriate.
- Vehicles start and end at the manufacturing plant.
- Multiple trips are possible for each vehicle.
- Demand quantities and delivery times are specified for each customer order.
- A customer order is serviced by a single vehicle (split delivery is not allowed).
- A single vehicle can deliver a product produced in separate production runs.
- The end of a customer's time window is the medicine usage time. A vehicle arriving before the customer's earliest allowed time waits until the time window begins. Late arrival after the time window is prohibited.
- Production quantities are determined accounting for the half-life of F-18 and the duration between production and delivery times.

The NMPDP also presents two sub-problems. Considering only the production scheduling component, it becomes a special type of bin packing problem, i.e., the production runs are modeled as bins and the customer orders are items. Since the production runs have different capacities, this problem becomes a variable-sized bin packing problem. Further, the size (production quantity) of items (customer orders) changes depending on the bin (production run) used. Thus, the production scheduling problem is a special case of the variable-sized bin packing problem (Pisinger & Sigurd, 2005).

The routing component, i.e., fixing the production schedule, becomes a vehicle routing problem with time windows (VRPTW). While vehicles leave the depot (production facility) at any time in a typical VRPTW, however, the embedded VRPTW in the problem specifies the ready times for the customer orders. The embedded VRPTW problem is similar to the pickup and delivery problem with time windows (PDPTW) (Dumas, Desrosiers, & Soumis, 1991; Lee, Ferdinand, Kim, & Ko, 2010).

3. Literature review

The nuclear medicine delivery problem resembles some perishable food and newspaper delivery problems. This section briefly reviews these studies and research efforts.

Tarantilis and Kiranoudis (2001) consider fresh milk distribution for a diary company in Athens, Greece, and propose a modified version of the threshold-acceptance algorithm of Dueck and Scheuer (1990), which is a deterministic version of the simulated annealing algorithm. Tarantilis and Kiranoudis (2001) treat the problem as a heterogeneous fixed fleet vehicle routing problem and do not consider customer time windows. Entrup, Gunther, Van Beek, Grunow, and Seiler (2005) develop three MIP models for production scheduling problems in yogurt production. They explicitly consider shelf-life in their models but do not consider delivery. Hsu, Hung, and Li (2007) and Osvald and Stirn (2008), who study the delivery of temperature-sensitive perishable food products, consider customer time windows, product value deterioration along delivery time, and time-dependent travel time, and formulate the problem as a mathematical model. Hsu et al. (2007) additionally consider time-varying temperature during the delivery day and propose a simple insertion heuristic to demonstrate the importance of the consideration of product value deterioration and energy cost in perishable product delivery.

Chen, Hsueh, and Chang (2009) study a production scheduling and vehicle routing problem with time windows for perishable food products but late delivery is allowed with a penalty. Each retailer has a stochastic demand with a known probability density function. The authors assume a single production line and that all products on the same vehicle are produced continuously as a single batch created on a particular production line. They present an integer nonlinear programming model for the problem, and propose a decomposition-based solution approach which uses the Nelder–Mead simplex algorithm (Nelder & Mead, 1965) for the production scheduling sub-problem and insertion and improvement algorithms for the vehicle routing sub-problem.

Garcia and Lozano (2004) study ready-mix concrete delivery. They classify the problem as scheduling with fixed start and end times. Raw materials at a plant are loaded into a revolving drum mounted on a vehicle which immediately delivers the mix to the customer site. The plant can mix up to a specified number (capacity) of customer orders at the same time. Since the plant has limited capacity, not all customer orders can be served. The authors consider two scenarios, arbitrary customer value and uniform customer value. They show that the first case corresponds to the fixed job scheduling problem and can be solved by a minimum cost flow algorithm. For the second case, they propose an exact graph-based algorithm and a branch-and-bound heuristic algorithm.

Mantel and Fontein (1993) develop a nonlinear mathematical programming model for designing a distribution network and routing solution for a Dutch regional newspaper. They use a location–allocation heuristic for determining the number of distribution centers and their locations and the savings algorithm of Clarke and Wright (1964) for truck route generation.

Ree and Yoon (1996) propose a solution method between three main distribution centers and 250 local distribution centers in Korea. They use a generalized assignment problem algorithm to assign the main centers to local centers and develop a simulated annealing algorithm that allows split deliveries. Song, Lee, and Kim (2002) use a regret distance method to assign three printing plants to 400 local distribution agents, a sweep-based method for route generation, and an urgent route first rule for route dispatching as the solution algorithms.

Hurter and Van Buer (1996) and Van Buer, Woodruff, and Olson (1999), who study a newspaper production and delivery problem with a single press, propose a nonlinear mathematical programming model and compare the performance of various tabu searches and simulated annealing algorithms. They also demonstrate that allowing multiple trips for a vehicle reduces operating costs. Russell, Chiang, and Zepeda (2008) consider a newspaper delivery problem and use a simple sequencing method based on the distance of zones from a newspaper printing plant for synchronizing production and truck loading, and a parallel insertion and tabu search method for the delivery routing problem. They report

[1] International Atomic Energy Agency (IAEA) suggests Type A packaging, which seals F-18 with a fiberboard box, a wooden box, and a steel drum filled with supplementary radiation-blocking materials. (IAEA, 2012, Cyclotron produced radionuclides: Guidance on Facility Design and Production of [^{18}F]Fluorodeoxyglucose(FDG), IAEA Radioisotopes and Radiopharmaceuticals Series No. 3).