Chemotherapy Operations Planning and Scheduling

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Chemotherapy operations planning and scheduling in oncology clinics is a complex problem due to several factors such as the cyclic nature of chemotherapy treatment plans, the high variability in resource requirements (treatment time, nurse time, pharmacy time) and the multiple clinic resources involved. Treatment plans are made by oncologists for each patient according to existing chemotherapy protocols or clinical trials. It is important to strictly adhere to the patient's optimal treatment plan to achieve the best health outcomes. However, it is typically difficult to attain strict adherence for every patient due to side effects of chemotherapy drugs and limited resources in the clinics. In this study, our aim is to develop operations planning and scheduling methods for chemotherapy patients with the objective of minimizing the deviation from optimal treatment plans due to limited availability of clinic resources (beds/chairs, nurses, pharmacists). Mathematical programming models are developed to solve chemotherapy operations planning and scheduling problem. A two-stage rolling horizon approach is used to solve these problems sequentially. Real-size problems are solved to demonstrate the effectiveness of the proposed algorithms in terms of solution quality and computational times.

Key words: Chemotherapy, planning, scheduling, oncology

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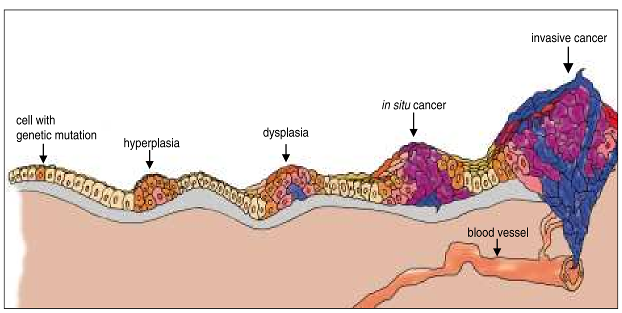
1. Introduction

Cancer is the second most common cause of death in the US, accounting for 26% of all deaths [2]. The National Cancer Institute estimates that approximately 11.1 million Americans with a history of cancer were alive in January 2005. Some of these individuals were cancer-free, while others still had evidence of cancer and may have been undergoing treatment [2]. In 2009, approximately 1.5 million new cancer cases are expected to be diagnosed in the US [2]. The National Institutes of Health estimates overall costs of cancer in 2008 at $228.1 billion; $93.2 billion for direct medical costs (total of all health expenditures), $18.8 billion for indirect morbidity costs (cost of lost productivity due to illness), and $116.1 billion for indirect mortality costs (cost of lost productivity due to premature death) [2].

Cancer is defined as a group of diseases characterized by uncontrolled growth and spread of abnormal cells [2]. Cancer has more than one hundred different types that vary in diagnostic detectability, state of cellular differentiation, rate of growth, invasiveness, metastatic potential and response to treatment [27]. The treatment decision is made according to the stage of the disease, expected survival rate, recurrence risk, and patient's health condition. A cancer's stage is based on the primary tumor size and whether it has spread to other areas of the body. Figure 1.a shows the stages of tumor growth. If cancer cells are present only in the layer of cells where they developed and have not spread, it is called *in situ* cancer. If cancer cells invade neighboring tissues and spread to other parts of the body through the blood and lymph systems, the tumor is said to be invasive/malignant.



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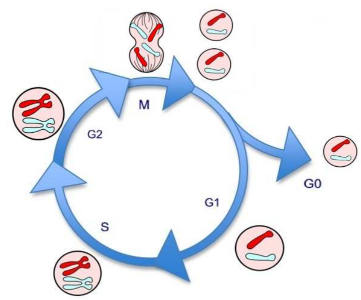
(a)



(b)

Figure 1 Tumor growth [6] and cell cycle (adapted from [21, 23])

Cancer is treated with different methods such as surgery, radiation, and chemotherapy. Surgery and radiotherapy are local treatments used to remove/kill small tumors or reduce the size of large tumors. In contrast, chemotherapy is a systemic approach that uses drugs to stop or slow tumor growth, control or prevent the spread of cancer cells, and/or relieve cancer symptoms such as pain (palliative chemotherapy). Chemotherapy drugs affect both normal and cancer cells by altering cellular activity during one or more phases of the cell cycle. The cell cycle includes five phases (G_0, G_1, S, G_2, M) during which the cell grows, replicates, and rests (see Figure 1.b). G_1 is the first growth phase where the cell prepares for DNA synthesis by producing RNA and protein. Synthesis of DNA occurs during the S phase, which is followed by a second period of growth, the G_2 phase. During G_2, synthesis of RNA and proteins continues as the cell prepares for division during the M

(mitosis) phase. After mitosis, the cell will either enter another cycle or await activation by resting in G_0 [4].

Chemotherapy drugs include both cell-cycle phase specific and cell-cycle phase non-specific drugs [4]. Cell-cycle phase specific drugs kill cells in a specific phase of the cell cycle. These types of drugs do not affect cells in the resting state [14]. They are most effective against cells that are rapidly dividing (especially when tumor size is small). Cell-cycle phase non-specific drugs affect cells in all phases of the cell cycle and are most effective against slow dividing cells (especially when tumor size is large). Chemotherapy treatment is given in cycles and a rest period is given between each cycle so that the number of normal cells increases and the body recovers. Several cycles of treatment are needed, as chemotherapy kills only a certain percentage of cancer cells [4]. The number and duration of the cycles depend on many factors such as cancer type, stage of the disease, and the general health of the patient. Treatment plans are developed by oncologists for each patient according to existing chemotherapy protocols or clinical trials.

In recent years, demand for chemotherapy has been increasing due to the aging population and more effective drugs. Warren et al. [30] analyzed the costs associated with surgery, chemotherapy, radiotherapy and hospitalizations for 306,709 persons aged 65 and older and diagnosed with breast, lung, colorectal, or prostate cancer. The proportion of cancer patients treated with chemotherapy increased from 15% to 21% between 1991 and 2002 [30]. The mean cost of chemotherapy has also increased significantly due to more effective, but more expensive drugs [30]. Mean lung cancer chemotherapy costs were the highest ($15,000) and increased by $8,173 per person treated between 1991 and 2002. Breast cancer chemotherapy costs increased an average of $6,160 over that period and by 2002 were $12,802 per person (yearly increase in cost $549).

Due to increased demand, oncology clinics experience higher workload that results in delays in laboratory, pharmacy, and chemotherapy administration areas. Waiting time for appointments, laboratory test results, and chemotherapy administration has been identified as a major source of patient dissatisfaction (Lis et al. [20]). Gesell et al. [15] analyzed the data from 5,907 cancer outpatients treated at 23 hospitals across the US and identified the top priorities for service improvement in outpatient cancer treatment facilities. The results indicate that reducing waiting times for the first visit and waiting times in the clinic for chemotherapy administration are among the highest priorities for quality improvement. Many studies indicate that well-designed scheduling can increase access to care, smooth clinic operations, increase patient satisfaction, improve quality of care, and reduce overall costs [1, 28]. Gruber et al. [16] studied data from an infusion clinic and found that appointment schedule that does not reflect the availability of resources is one of the most frequent cause of delay. Chabot and Fox [8] developed a patient classification system that estimated patient care needs and nursing care time for the volume of patients and diversity of treatments that occurred in an outpatient chemotherapy unit. The classification system allowed realistic scheduling of patient appointments. Dobish [13] proposed a next-day chemotherapy schedule, with laboratory and physician appointments on one day and chemotherapy administration is on the next day. The implementation of this next–day chemotherapy administration schedule resulted in improved efficiencies for pharmacy and nursing and decreased in-clinic waiting times for patients.

Most previous studies propose using scheduling templates/rules based on nursing or pharmacy times (Langhorn and Morrison [18], Diedrich and Plank [12], Hawley and Carter [17]). The scheduling decisions are made in an ad-hoc manner according to physician and scheduler experiences and patient preferences. To the best of our knowledge, there is no study that proposes optimization methods to schedule chemotherapy treatments optimizing several objectives such as minimization of treatment delay, patient waiting time and staff overtime, and maximization of staff utilization. In this paper, we develop planning and scheduling methods for chemotherapy patients with the objective of decreasing patient waiting time and maximizing adherence to treatment plans, while considering the limited availability of clinic resources (beds/chairs, nurses, pharmacists). This study differs from previous studies in that it develops and uses optimization methods rather than scheduling templates and ad-hoc rules.

The paper is structured as follows. Section 2 explains the chemotherapy planning and scheduling problem in detail. Section 3 presents a mathematical programming model, and section 4 presents a two-stage algorithm to solve planning and scheduling problems sequentially. Section 5 presents a variety of computational studies to illustrate the effectiveness of the proposed algorithms, and Section 6 provides some concluding remarks and discusses future work.

2. Problem characteristics

Chemotherapy planning and scheduling in oncology clinics is a complex problem due to several factors such as the cyclic nature of treatment plans, high variability in treatment times, and multiple clinic resources involved. Chemotherapy treatment is given in cycles with rest periods during and between each cycle. The number and duration of the cycles change according to cancer type and stage of the disease. It is important to strictly adhere to the patients prescribed treatment plan to achieve the best health outcomes. However, it is typically difficult to attain strict adherence due to clinic/patient scheduling complexities, side effects of the chemotherapy drugs, and limited resources in the clinics. Multiple resources such as pharmacists, phlebotomy staff, chemotherapy nurses, chairs, etc. are required for chemotherapy administration. The treatment lengths, nursing and pharmacy times show high variability according to the cancer type, patient condition, and number of drugs used. Nurse workflow varies for different treatments according to the number of drugs, infusion method, and risk of side effects. Nurse workflow may become complicated for treatment regimens with multiple drugs and high risk of side effects. It is important to consider the availability of all resources and complex workflow of chemotherapy nurses for safe administration of chemotherapy.

This work develops planning and scheduling methods for chemotherapy patients in oncology clinics. We define the planning problem as the allocation of patient treatments to days with the objective of minimizing unnecessary delays due to limited resources and under-utilization and over-utilization of resources, and the scheduling problem as the determination of appointment times for chemotherapy patients on each day with the objective of minimizing patient staff idle time, and overtime. This problem is more difficult than the classical appointment scheduling problems, which consider a single resource and one type of patient with similar service time requirements. The problem characteristics are explained in detail in the following subsections.

2.1. Chemotherapy treatment

Chemotherapy treatment plans are developed by oncologists for each patient according to existing chemotherapy protocols and the patient's condition. Chemotherapy protocols show the types of drugs, doses, and schedule of drugs based on the type of cancer, stage of cancer, and other specifics about the person's cancer (a comprehensive list of protocols can be found on the National Comprehensive Cancer Network (NCCN) website [22]). Table 1 shows a sample chemotherapy regimen (BEP) with three drugs. CISplatin is administered intravenously (IV) over 30 minutes on Days 1-5. Etoposide is administered intravenously over 60 minutes on Days 1-5. Bleomycin is administered intravenously over 30 minutes on Days 1, 8, and 15. The administration time is 120 minutes on Day 1 and 90 minutes on Days 2-5, and 30 minutes on Days 8 and 15. Pre-medication might be required for hypersensitivity before Bleomycin, which adds 30-60 minutes to the administration time on Days 1, 8, and 15. No treatment is given on days 6-7, 9-14, and 16-21. The 21-day cycle is repeated 2 to 4 times. It is important to adhere to the patient's treatment plan to achieve the best results, since delaying the treatment reduces the dose intensity and hence decreases its effectiveness. Leonard et al. [19] shows that a 7-day delay in chemotherapy delivery reduces the dose intensity by 5%. Many other studies show the correlation between low dose intensity and poor health outcomes (i.e. decreased tumor growth control, poorer quality of life, and shortened overall survival) [5, 7, 9, 26, 31].

Days	Drugs	Dose	Treatment
1	CISplatin, Etoposide, Bleomycin	20 mg/m^2, 100 mg/m^2, 30 units	IV over 30, 60, 30 minutes
2-5	CISplatin, Etoposide	20 mg/m^2, 100 mg/m^2	IV over 30, 60 minutes
6-7	Rest		
8	Bleomycin	30 units	IV over 30 minutes
9-14	Rest		
15	Bleomycin	30 units	IV over 30 minutes
16-21	Rest		

Table 1 A sample chemotherapy regimen [29]

2.2. Resources in the chemotherapy treatment environment

In the last two decades, chemotherapy administration has shifted from the inpatient setting to the outpatient setting due to sophisticated delivery methods, new oral preparations of drugs, and improved management of side-effects, enabling patients to tolerate their treatments without being hospitalized. The administration of chemotherapy in the outpatient setting has the inherent challenge of time constraints (Chabot and Fox [8]), that is, outpatient clinics treat patients during working hours and patients do not stay overnight.

Chemotherapy treatment requires several resources. Table 2 provides the human resources and their tasks. Besides clinic staff, chemotherapy treatment requires resources such as chairs, beds and equipment (ports, pumps, IVs, etc.). The availability of resources determines the capacity of the clinic. Actually determining the capacity is a complex issue [3] due to high variability in treatment lengths, nursing and pharmacy times. For example, in an oncology clinic, the number of chairs and beds can be used as the maximum capacity and patients can be scheduled based on their treatment times and availability of chairs/beds. However, the number of nurses may not be sufficient to staff all the chairs/beds. Sometimes, the chairs/beds might be fully utilized, but the nurses might be idle due to varying nursing times for each treatment. In this study, we seek to minimize the overtime and idle time of clinic staff while making planning and scheduling decisions.

Staff	Tasks
Administrative staff	Manage the clinic
Patient service assistants	Register the patient
Medical assistants	Prepare patient documentation and provide supportive care
Pathology staff	Perform lab tests
Oncologists	See patients to evaluate patients' health and make treatment decisions
Pharmacy staff	Prepare chemotherapy regimens
Portering staff	Transport specimens, chemotherapy drugs
Chemotherapy nurses	Administer chemotherapy to patients

Table 2 Oncology clinic staff and their tasks

The flow of chemotherapy patients in an oncology clinic is shown in Figure 2. All patients arrive to the clinic by appointment. The patient service assistant (PSA) registers the patient. The medical assistant (MA) prepares patient charts and takes vitals. The phlebotomy staff draws blood for laboratory tests. If the patient has a port (device inserted under the skin of the patient by surgical procedure to facilitate the blood drawing process), these tasks are performed by a nurse. The patient waits in the waiting room until the laboratory results become available. Sometimes, the patient has his/her blood drawn and analyzed in another clinic prior to the infusion appointment. In that case, there will be no phlebotomy work in the oncology clinic. The oncologist checks laboratory results and sees the patient. If the patient's health is suitable for the treatment, she/he is sent to the infusion clinic for a same-day treatment or an appointment is scheduled for chemotherapy administration at a later date. If the patient has not totally recovered, the oncologist may delay the treatment until the patient becomes ready for the treatment. When the patient comes to the infusion clinic, he/she waits for an available chair/bed and nurse. When these become available, the chemotherapy nurse takes the patient to the chair/bed. The pharmacy staff prepares the chemotherapy drugs. The portering staff transports the drugs from pharmacy to the clinic. Chemotherapy nurses administer the chemotherapy to the patient.

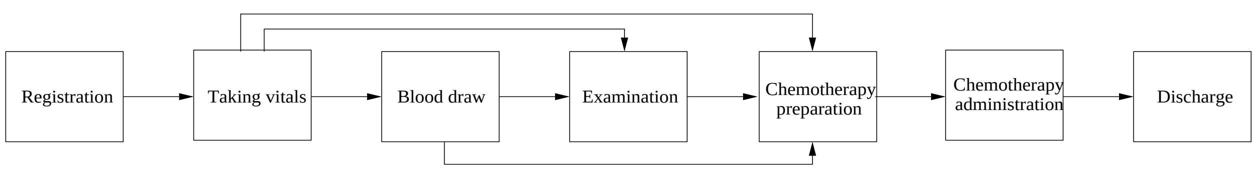


Figure 2 Patient Flow

2.3. Chemotherapy administration

Chemotherapy nurses play an essential role in administering chemotherapy, managing side-effects, stabilizing patients during an emergency, documenting important information in patient charts, providing counseling to patients and family members, and triaging patient questions and problems [24]. During chemotherapy administration, nurses do not have to be constantly with the patient, and they can handle more than one patient simultaneously. Nurse workflow varies by treatment according to the number of drugs, infusion method and risk of side effects. The number of patients that can be handled simultaneously changes according to the difficulty of the administration. Regimens with only one drug and one or no pre-medications may require less time than a multi-drug regimen with multiple pre-medications and higher risk of side effects. Table 3 shows the difference between estimated nursing times and treatment times for three regimens. For example, Rituximab (shown in Table 3) is a single drug regimen, in which eight hours is required for the overall treatment. The nurse starts the infusion, increases the infusion rate every 30 minutes, and observes the patient for any side effects during all dose increases and after the infusion is completed. The nurse flow may become more complicated when there are multiple drugs that must be infused sequentially. It is important to have a reasonable nurse workload for several reasons such as patient safety, quality of care, patient and staff satisfaction.

Regimen	Regimen characteristics	Treatment time	Nursing time
Gemcitabine	Single agent Low risk for side effects No special monitoring required Infused in less than 60 minutes	2 hours	30 minutes
Rituximab, first dose	Potential for hypersensitivity reactions Requires more than routine vital signs and observation Requires titration every 30 minutes	8 hours	60 minutes
5-fluorouracil, epirubicin, cyclophosphamide	Multi-drug regimen Vesicant administration protocol in multiple syringes	2 hours	90 minutes

Table 3 Estimated treatment times and nursing times for three regimens: Gemcitabine, Rituximab (first dose), and 5-fluorouracil, epirubicin, cyclophosphamide (Chabot and Fox [8])

Patient acuity systems are used in inpatient and nursing home settings to assess patient care needs and find appropriate staffing levels. Even though there is high variability in patient care needs for different chemotherapy treatments, there are few studies that propose using an acuity system in oncology clinics. Cusack et al. [10] propose a patient intensity system that reflects the severity of patient illness/need and the complexity of service required in an ambulatory oncology research center. Chabot and Fox [8] develop a patient classification system that estimates patient care needs and nursing care time in an outpatient chemotherapy unit. Delaney et al. [11] propose a chemotherapy basic treatment equivalent model, which includes the various factors that affect treatment duration. We consider the treatment acuity levels to find the maximum number of patients that can be assigned to a nurse while scheduling the patients.

3. Mathematical programming models

Table 4 provides notation that will be used throughout the paper. We assume that the treatment plan (cycle length, C_i, number of times a cycle will be repeated, F_i, and the length of treatment on each day, r_{id}) is known for each patient. This is a realistic assumption since chemotherapy treatments are planned by oncologists and schedulers determine the appointment times based on known treatment plans. If the oncologist changes the treatment plan for an existing patient, the patient is scheduled based on new treatment plan. The effect of treatment delays changes according to cancer type, stage of the disease and the patient's health. We use priorities (w_i^d) for each patient i to incorporate the effect of treatment delays. As w_i^d increases, the negative effect of treatment delay on patient's health increases.

We assume there are new patients waiting for their treatment to start (P^N) and existing patients who are already in their treatment cycles (P^E). The planning problem is to assign the cycle of treatments to a sequence of days for each patient. The scheduling problem is finding appointment times for all patients on their assigned days. The planning problem is solved for a number of weeks or months. The planning horizon (T) is divided into days, and days are divided into smaller time slots (S) to find the appointment days and times for patients.

The oncology clinic has limited resources. The number of chairs/beds (K) and other equipment determine the fixed capacity of the clinics. The clinic staff (nurses, pharmacists, etc.) who provide care determine the flexible capacity. Thus, the capacity can be increased by increasing the number of nurses (N_t) or working overtime. However, increasing the number of nurses and working overtime will increase the cost, since staff are paid more than the regular rate when they work after clinic hours. When the clinic resources are not fully utilized, the idle time can be thought of as lost capacity and reduced access to care. We assume that the number of nurses and their normal working hours (H_t) are given for each day in the planning horizon.

As discussed in Section 2.3, the workflow of chemotherapy nurses is complicated. Considering only the total number of patients assigned to each nurse does not reflect the actual workload of the nurses throughout the day. If patients with high acuity levels are assigned to the same nurse, there may be delays in treatments and probability of making errors increases because of heavy workload. We consider acuity levels (a_{id}) for different treatment types to achieve a well-balanced workload for nurses. The acuity levels can be determined by nurse input or by performing time studies and analyzing the time spent for all treatment-related tasks. We assume an upper bound threshold (A^{max}) on the amount of acuity that can be assigned to a single nurse, thus the maximum number of patients that can be assigned depends on the acuity mix. We assume that a nurse can start at most one treatment per slot since he/she must carefully assess the patient, check dosages, and start the treatment.

P^N, P^E	Set of new and existing patients ($i \in P^N \cup P^E$ and $P^N \cap P^E = \emptyset$)
P^R	Set of patients who are referred to receive chemotherapy in the last planning period ($P^R \subset P^N$)
P^O	Set of patients whose treatment cycles have terminated in the last planning period ($P^O \subset P^E$)
P^{NE}	Set of patients whose treatments have started in the last planning period ($P^{NE} \subset P^N$)
C_i	Cycle length of the treatment for patient i (in days) ($d = 1 \cdots C_i$)
F_i	Number of cycles that will be repeated for patient i ($f = 1 \cdots F_i$)
K	Number of chairs ($k = 1 \cdots K$)
T	Length of planning horizon (days) ($t = 1 \cdots T$)
Δ	Re-planning frequency (days) ($\Delta < T$)
N_t	Number of nurses on day t ($j = 1 \cdots N_t$)
U	Target nurse utilization
S	Number of slots on each day ($s = 1 \cdots S$)
H_t	Number of regular working hours on day t
w^o	Cost of overtime
w^u	Cost of idle time
w_i^d	Effect of treatment delay on patient i
r_{id}	Treatment length on day d of each cycle for patient i ($d = 1 \cdots C_i$)
a_{id}	Acuity level on day d of each cycle for patient i ($d = 1 \cdots C_i$)
est_i	Earliest treatment start day for patient i
A^{max}	Maximum acuity level a nurse can handle at any time
X_{it}	Binary variable, 1 if the treatment of patient i starts on day t, 0 otherwise
R_{it}	Treatment time required for patient i on day t
A_{it}	Acuity level of patient i on day t per unit time ($A_{it} = \{1, 2, 3, ...\}$)
B_{it}	Total acuity of patient i on day t, i.e. $R_{it}A_{it}$
P_t	Set of patients who have treatment on day t, i.e. $P_t = \{i : R_{it} > 0\}$
G_t^o	Over utilization on day t
G_t^u	Under utilization on day t
C_t^{max}	Completion time of all treatment on day t
Y_{ijkst}	Binary variable, 1 if the treatment of patient i is started by nurse j on chair k at time slot s on day t, 0 otherwise
M_{jt}	Completion time of all treatments assigned t nurse j on day t

Table 4 Notation

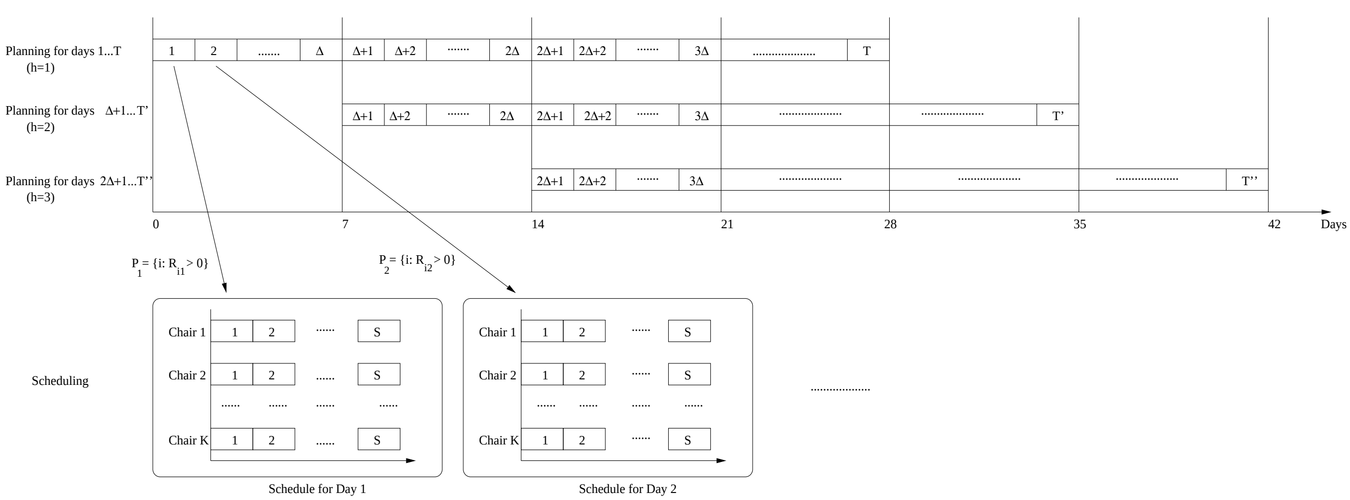


Figure 3 Chemotherapy operations planning and scheduling

We proposed a two-stage algorithm to solve the chemotherapy operations planning and scheduling problems sequentially. At Stage 1, the planning problem is solved to find the treatment start days of the patients (X_{it}), which is the first day of the first cycle. Since the treatment plan for each patient is known, the treatment days ($t' = t + f \cdot C_i + d - 1$), resource requirements (R_{it}) and acuity levels (A_{it}) are also determined at this stage. At Stage 2, the daily scheduling problem is solved for the given set of patients assigned to the same day. Patients are assigned to chairs, nurses, and appointment times. Figure 3 illustrates the two-stage algorithm to solve planning and scheduling problems.

Two integer programming models are proposed to solve the planning and scheduling problems sequentially. The planning problem is as follows:

$$(\text{IP}_1) \quad min \quad \sum_{t=1}^{T}(w^o G_t^o + w^u G_t^u) + \sum_{i \in P^N}\sum_{t=1}^{T} w_i^d (t - est_i) X_{it} \tag{1}$$

$$st \quad \sum_{t=1}^{T} X_{it} \leq 1 \qquad \forall i \in P^N \tag{2}$$

$$R_{it} = \sum_{f=1}^{F_i}\sum_{d=1}^{C_i} r_{id} X_{i,t-(f-1)C_i-d+1} \qquad \forall i \in P^N, t = 1 \cdots T \tag{3}$$

$$A_{it} = \sum_{f=1}^{F_i}\sum_{d=1}^{C_i} a_{id} X_{i,t-(f-1)C_i-d+1} \qquad \forall i \in P^N, t = 1 \cdots T \tag{4}$$

$$B_{it} = \sum_{f=1}^{F_i}\sum_{d=1}^{C_i} r_{id} a_{id} X_{i,t-(f-1)C_i-d+1} \qquad \forall i \in P^N, t = 1 \cdots T \tag{5}$$

$$G_t^o - G_t^u = \sum_{i \in P^N \cup P^E} R_{it} - K \cdot H_t \qquad t = 1 \cdots T \tag{6}$$

$$\sum_{i \in P^N \cup P^E} B_{it} \leq U N_t H_t A^{max} \qquad t = 1 \cdots T \tag{7}$$

$$X_{it} \in \{0, 1\} \qquad \forall i \in P^N, t = 1 \cdots T \tag{8}$$

The objective is to minimize total staff overtime and idle time, and total treatment delay. The first term in the objective function is total overtime and idle time cost of clinic staff. The second term is the total weighted treatment delay, which is calculated according to the earliest treatment start time (est_i) and planned treatment start time ($\sum_t t X_{it}$). The earliest treatment start time is determined by the oncologist and depends on the patient's health status, the treatment plan and other treatments (surgery, radiotherapy) that needs to be coordinated with chemotherapy. The delays are multiplied by w_i^d to incorporate the differences among treatments in terms of their effect on health outcomes. The patient's treatment will start on at most one of the days in the planning horizon, which is guaranteed by constraint (2). If the planning horizon is not long enough and the number of patients is high, then the treatment may not start in the planning horizon. The resource requirement (treatment time, nurse time, pharmacy time) and acuity level per unit time for each patient on a given day after the treatment start (a patient's acuity level is positive only on appointment days, zero otherwise) are calculated in constraints (3) and (4). Total acuity level of patient i on a day is calculated by constraint (5). For example, for patient i^* with cycle length of 21 days ($C_{i^*} = 21$), treatment on days 1 and 3 of each cycle (treatment length on day 1 is $r_{i^*1} = 90$, acuity level on day 1 is $a_{i^*1} = 2$, treatment length on day 3 is $r_{i^*3} = 60$, acuity level on day 3 is $a_{i^*3} = 1$, treatment length and acuity levels on days 2, 4–21 are zero), and two cycles ($F_{i^*} = 2$), constraints (3)–(5) would be as follows:

$$
\begin{array}{lcll}
R_{i^*1} & = & 90X_{i^*t} & t = 1,2 \\
R_{i^*t} & = & 60X_{i^*,t-2} + 90X_{i^*t} & t = 3\cdots 21 \\
R_{i^*t} & = & 90X_{i^*t-21} + 60X_{i^*t-2} + 90X_{i^*t} & t = 22,23 \\
R_{i^*t} & = & 60X_{i^*,t-23} + 90X_{i^*,t-21} + 60X_{i^*t-2} + 90X_{i^*t} & t = 24\cdots T \\
 & & & \\
A_{i^*1} & = & 2X_{i^*t} & t = 1,2 \\
A_{i^*t} & = & 1X_{i^*,t-2} + 2X_{i^*t} & t = 3\cdots 21 \\
A_{i^*t} & = & 2X_{i^*t-21} + 1X_{i^*t-2} + 2X_{i^*t} & t = 22,23 \\
A_{i^*t} & = & 1X_{i^*,t-23} + 2X_{i^*,t-21} + 1X_{i^*t-2} + 2X_{i^*t} & t = 24\cdots T \\
 & & & \\
B_{i^*1} & = & 180X_{i^*t} & t = 1,2 \\
B_{i^*t} & = & 60X_{i^*,t-2} + 180X_{i^*t} & t = 3\cdots 21 \\
B_{i^*t} & = & 180X_{i^*t-21} + 60X_{i^*t-2} + 180X_{i^*t} & t = 22,23 \\
B_{i^*t} & = & 60X_{i^*,t-23} + 180X_{i^*,t-21} + 60X_{i^*t-2} + 180X_{i^*t} & t = 24\cdots T
\end{array}
$$

Constraint (6) is used to calculate the overtime and idle time. Since the appointment times are not determined in the planning part, the overtime and idle time are approximate values based on total available capacity ($K \cdot H_t$). Constraint (7) is used to control the total acuity of the patients assigned to nurses on each day. The maximum total acuity than can be assigned to nurses during normal working hours is $N_t H_t A^{max}$. However, this is an over-estimate, because it does not consider that a nurse can start at most one treatment at any slot. Therefore, we multiply the maximum total acuity level by U. As will be explained later, the value of U should be selected carefully in order not to overload nurses. Constraints (6) and (7) are necessary to make a reasonable number of assignments to days based on available capacity.

The proposed model finds the treatment days, resource requirement and acuity level on each treatment day for new patients. The resource requirements and acuity levels for existing patients were already calculated in previous time periods and are used as inputs in the proposed model to calculate the overtime and idle time. The resource requirements (R_{it}) and acuity levels (A_{it}) for all patients ($i \in P^N \cup P^E$) are used as inputs to the scheduling problem. The integer programming model proposed to solve the scheduling problem is as follows:

$$(\text{IP}_2) \quad min \quad \sum_{t=1}^{T} C_t^{max} \tag{9}$$

$$st \quad \sum_{j=1}^{N_t} \sum_{k=1}^{K} \sum_{s=1}^{S-R_{it}+1} Y_{ijkst} = 1 \qquad \forall i \in P_t, t = 1 \cdots T \tag{10}$$

$$\sum_{i \in P_t} \sum_{j=1}^{N_t} \sum_{u=max\{s-R_{it}+1,1\}}^{min\{S-R_{it}+1,s\}} Y_{ijkut} \le 1 \qquad k = 1 \cdots K, s = 1 \cdots S, t = 1 \cdots T \tag{11}$$

$$\sum_{i \in P_t} \sum_{k=1}^{K} \sum_{u=max\{s-R_{it}+1,1\}}^{min\{S-R_{it}+1,s\}} A_{it} Y_{ijkut} \le A^{max} \qquad j = 1 \cdots N_t, s = 1 \cdots S, t = 1 \cdots T \tag{12}$$

$$\sum_{i \in P_t} \sum_{k=1}^{K} Y_{ijkst} \le 1 \qquad j = 1 \cdots N_t, s = 1 \cdots S, t = 1 \cdots T \tag{13}$$

$$\sum_{k=1}^{K} \sum_{s=1}^{S-R_{it}+1} Y_{ijkst}(s + R_{it} - 1) \le M_{jt} \qquad \forall i \in P_t, j = 1 \cdots N_t, t = 1 \cdots T \tag{14}$$

$$M_{jt} \le C_t^{max} \qquad j = 1 \cdots N_t, t = 1 \cdots T \tag{15}$$

$$Y_{ijkst} \in \{0, 1\} \qquad \forall i \in P_t, j = 1 \cdots N_t, \; k = 1 \cdots K, s = 1 \cdots S, t = 1 \cdots T \tag{16}$$

The objective is to minimize the total completion time of all treatments on day t. Each patient who has treatment on day t ($i \in P_t$) is assigned to a nurse, a chair, and a time slot by constraint (10). Constraint (11) ensures that at most one patient is assigned to a chair. The total acuity level assigned to a nurse cannot exceed the maximum acuity level, which is controlled by constraint (12). Constraint (13) ensures that a nurse can start at most one treatment per slot. The total completion time of the treatments assigned to a nurse on a given day is calculated in constraint (14). The total completion time of all treatments for each day is calculated in constraint (15). Constraint (16) is the integrality constraint. The proposed model IP_2 can be decomposed into smaller subproblems for each day t. The subproblems can be solved independently to find the appointment times, nurses and chairs on each day.

The proposed integer programming models can be solved optimally. However, the length of the planning horizon, number of time slots on each day, and number of patients, nurses and chairs affect the computational complexity of the problem. The first model (IP_1) has $|P^N| \times T$ binary variables, $3|P^N| \times T + T$ continuous variables, and $|P^N| + 3|P^N| \times T \times \max_i\{C_i F_i\} + 2T$ constraints. The second model (IP_2) has $|P_t| \times N_t \times K \times S$ binary variables, and $|P_t| + K \times S + 2N_t \times S + |P_t| \times N_t + N_t$ constraints for a given day t. Please note that the second model is solved for all days in the planning horizon. If the number of slots, patients, chairs, and nurses are 40, 50, 20, and 7, respectively, then there will be 280,000 binary variables and 8,687 constraints in IP_2 for each day.

In order to reduce the computational burden, we propose a heuristic ($ALTT_t$) to find a feasible solution for the scheduling problem. This schedule can be used as an initial feasible solution while solving IP_2 optimally. The basic steps of the algorithm is as follows:

Algorithm 1 $ALTT_t$: Longest treatment time first rule incorporating acuity levels

1: $NurseAvail_{jst} = 0$, $ChairAvail_{kst} = 0$, $TreatStart_{jst} = 0$, $M_{jt} = 0$
2: Sort all patients according to their treatment times, i.e. $R_{it} \geq R_{i+1,t}$
3: **for all** $i = 1$ to I **do**
4:   **for all** $s = 1$ to S, $j = 1$ to J and $k = 1$ to K **do**
5:     Assign patient i to nurse j, chair k and slot s temporarily
6:     **if** $NurseAvail_{j,s',t} + A_{it} \leq A^{max}$, $TreatStart_{j,s,t} < 1$ and $ChairAvail_{j,s',t} < 1$ for all k, j, s and s' where $s' \geq s$ and $s' < s + R_{it}$ and given t **then**
7:       Go to Step 9
8:     **end if**
9:     (s, j, k) satisfies the constraints (6), (7) and (8). Go to Step 11.
10:   **end for**
11:   $(s^*, j^*, k^*) = (s, j, k)$ and $Y_{i,j^*,k^*,s^*,t} = 1$
12:   $TreatStart_{j^*,s^*,t} = 1$
13:   **for all** $s' \geq s^*$ and $s' \leq s^* + R_{it} - 1$ **do**
14:     $NurseAvail_{j^*,s',t} = NurseAvail_{j^*,s',t} + A_{it}$
15:     $ChairAvail_{j^*,s',t} = 1$
16:   **end for**
17:   **if** $s^* + R_{it} - 1 > M_{j^*,t}$ **then**
18:     $M_{j^*,t} = s^* + R_{it} - 1$
19:   **end if**
20:   **if** $M_{j^*,t} > C_t^{max}$ **then**
21:     $C_t^{max} = M_{j^*,t}$
22:   **end if**
23: **end for**

At Step 1, $NurseAvail_{jst}$, $ChairAvail_{kst}$, and $TreatStart_{jst}$ are initialized as zero. If $NurseAvail_{jst}$ is zero, that means nurse j is available at slot s on day t. If $ChairAvail_{kst}$ is zero, that means chair/bed k is available at time slot s on day t. When $TreatStart_{jst}$ is zero, nurse j can start a treatment at slot s on day t. The completion time of all patients assigned to nurse j on day t (M_{jt}) is also initialized to zero at Step 1. At Step 2, the patients are sorted in non-increasing order of their treatment times (R_{it}). Each patient in the sorted list is assigned to a nurse, a chair/bed and a time slot (j, k, s) temporarily at step 5. At Step 6, it is checked whether constraints (6), (7) and (8) are satisfied. If all constraints are satisfied, then the patient is assigned to the corresponding nurse, chair/bed and slot (Step 11). At Steps 12–16, $TreatStart_{jst}$, $NurseAvail_{jst}$, and $ChairAvail_{kst}$ are updated. At Steps 17–19, the completion time of all patients assigned to a nurse on day t (M_{jt}) is updated. At Steps 20–22, the completion time of all treatments on day t is calculated.

The proposed algorithm is similar to longest processing time (LPT) rule, which is used to minimize makespan in parallel machine scheduling [25]. The LPT rule is modified to control the total acuity level and number of treatment starts assigned to each nurse. The number of slots is chosen as large as possible so that all patients can be assigned to nurses, chairs/beds and time slots. The proposed algorithm aims to minimize the completion time of all patients.

Another way to reduce the computational complexity of IP_2 is considering a single resource rather than considering both resources (chairs and nurses). For example, if the nurses' time is the limiting resource, as appears to be the case in most of the clinics, the chair assignment can be removed from the model. The index k for chairs and constraint (11) are removed from the model to have a smaller size problem with $|P_t| \times N_t \times S$ binary variables, and $|P_t| + 2N_t \times S + |P_t| \times N_t + N_t$ constraints for a given day t. The patients should be assigned to chairs after the following integer programming model (IP_3), which is used to assign patients to nurses and to find appointment times, is solved.

$$(\text{IP}_3) \quad min \quad \sum_{t=1}^{T} C_t^{max} \tag{9}$$

$$st \quad \sum_{j=1}^{N_t} \sum_{s=1}^{S-R_{it}+1} Y_{ijst} = 1 \qquad \forall i \in P_t, t = 1 \cdots T \tag{10'}$$

$$\sum_{i \in P_t} \sum_{u=max\{s-R_{it}+1,1\}}^{min\{S-R_{it}+1,s\}} A_{it} Y_{ijut} \leq A^{max} \qquad j = 1 \cdots N_t, s = 1 \cdots S, t = 1 \cdots T \tag{12'}$$

$$\sum_{i \in P_t} Y_{ijst} \leq 1 \qquad j = 1 \cdots N_t, s = 1 \cdots S, t = 1 \cdots T \tag{13'}$$

$$\sum_{s=1}^{S-R_{it}+1} Y_{ijst}(s + R_{it} - 1) \leq M_{jt} \qquad \forall i \in P_t, j = 1 \cdots N_t, t = 1 \cdots T \tag{14'}$$

$$M_{jt} \leq C_t^{max} \qquad j = 1 \cdots N_t, t = 1 \cdots T \tag{15'}$$

$$Y_{ijst} \in \{0, 1\} \qquad \forall i \in P_t, j = 1 \cdots N_t, \; s = 1 \cdots S, t = 1 \cdots T \tag{16'}$$

The planning and scheduling problems are solved for the patients who need treatment for several weeks. The schedules cannot be fixed for the whole planning horizon. New patients with different acuity levels and treatment plans are referred to receive chemotherapy treatment and they should be added to the existing schedule. The planning problem should be solved frequently to minimize treatment delays for new patients. We use a rolling horizon approach to solve planning and scheduling problems sequentially. The proposed method is explained in detail in the following section.

4. Rolling horizon methodology

We propose a rolling horizon approach to solve planning and scheduling problems with the objective of minimizing treatment delays for new patients. We solve the planning problem every Δ days for a planning horizon of T days. The planning problem finds the treatment start days for the new patients for the first Δ days starting from current time (t^c). No treatment start is planned for time periods $t^c + \Delta + 1, \cdots, T$. The detailed appointment schedule is generated only for the first Δ days. After the schedule for Δ days is executed, the planning and scheduling problems are solved for time periods $t^c + \Delta + 1, \cdots, t^c + \Delta + T$. The planning horizon T should be updated every time the planning problem is solved because the set of new patients change. The patients whose treatments have started in the last Δ days (P^{NE}) are removed from the set of new patients. The patients who are referred to receive chemotherapy in the last Δ days (P^R) are added to the set. The set of existing patients also changes. The patients in set P^{NE} are added to the set of existing patients and the patients whose treatment cycles terminate in the last Δ days (P^O) are removed from the set. The planning horizon T is calculated according to the total treatment length of new patients and the treatment completion time of existing patients, i.e. $T = \max\{t^c + \Delta + \max_{i\in P^N}\{C_iF_i\}, \max\{t : R_{it} > 0, i \in P^E\}\}$. The first term is the maximum treatment completion time for the new patients. The second term is the treatment completion time for all existing patients. The treatment length of a new patient is calculated by multiplying the cycle length (C_i) with number of cycles (F_i). The treatment completion time of an existing patient i is the last time period that the patient is treated and is calculated as $\max\{t : R_{it} > 0\}$.

The following algorithm gives the basic steps of a rolling horizon approach:

Algorithm 2 Rolling horizon algorithm

1: Initialize $t^c = 0$.
2: Calculate the planning horizon for the given set of existing (P^E) and new patients (P^N).
   $T = \max\{t^c + \Delta + \max_{i\in P^N}\{C_iF_i\}, \max\{t : R_{it} > 0, i \in P^E\}\}$.
3: Solve IP_1 for all patients in $P^E \cup P^N$ and the planning horizon of $[t^c + 1, T]$.
4: **for all** $t = t^c + 1, t^c + 2, \cdots, t^c + \Delta$ **do**
5: Determine the set of patients who have treatment on day t.
   $P_t = \{i : R_{it} > 0$ and $i \in P^E \cup P^N\}$.
6: Solve IP_2 (or IP_3) for day t.
7: **end for**
8: Find sets P^{NE}, P^O and P^R.
   $P^{NE} = \{i : X_{it} = 1, t \in [t^c + 1, t^c + \Delta], i \in P^N\}$
   $P^O = \{i : \max\{t : R_{it} > 0\} \in [t^c + 1, t^c + \Delta]\}$
   $P^R = \{i : est_i \in [t^c + 1, t^c + \Delta]\}$
9: Update P^E and P^N.
   $P^E = P^E \cup P^{NE} \setminus P^O$
   $P^N = P^N \cup P^R \setminus P^{NE}$
10: Increase t^c by Δ and go to Step 2.

At Step 1, the current time is initialized to zero. The set of existing patients (P^E) and new patients (P^N) are assumed to be known at time zero. At Step 2, the planning horizon T is calculated according to the treatment completion times of existing patients and maximum completion time of new patients. The planning problem IP_1 is solved at Step 3. The treatment start times are found for the time interval $[t^c + 1, t^c + \Delta]$. The scheduling problem is solved for each day $t \in [t^c + 1, t^c + \Delta]$ at Step 6. According to the solution of the planning problem, patients whose treatments have started (P^{NE}) and whose treatment cycles have terminated (P^O) during time interval $[t^c + 1, t^c + \Delta]$ are found at Step 8. The set of patients who are referred to receive chemotherapy are also found at this step. At Step 9, the sets of existing and new patients are updated. The schedules for time periods $t^c + 1 \cdots t^c + \Delta$ are executed and the current time is updated at Step 10. Steps 2– 10 are repeated every Δ days.

We present a numerical example to clarify the basic steps of the rolling horizon approach. Assume that there are two nurses ($N_t = 2$) and five chairs ($K = 5$) in an infusion clinic. Four hours is used as the normal working hours. The total working hours is 20 hours ($KH_t = 5 \times 4 = 20$ hours $=$ 1200 minutes). Δ is chosen as seven days, which corresponds to a week. Table 5 shows the sets that are used at the beginning of weeks 11 and 12. At the beginning of week 11, the sets P^E and P^N are given in the first row of the table. The planning problem is solved to assign new patients to days 71–75. The treatment times of the existing patients are used to calculate the remaining capacity for each day. The total treatment times of the existing patients on days 71–75 are 1155, 1185, 675, 555, 300 minutes. The clinic is closed at weekends, therefore no patient is scheduled on days 76–77. The treatment start days for new patients 107, 98, 109, 110, 97, 103, 105, 106, 100, 101, and 104 are 71, 73, 73, 73, 74, 74, 74, 74, 75, 75, and 75, respectively. At week 11, the treatments of patients 4, 11, 13, 43, 76 (P^O) are terminated. Ten new patients ($P^R = \{111, 112, ..., 120\}$) are referred to receive treatment. At the beginning of week 12, sets of existing and new patients are updated as $P^E = P^E \cup P^R \setminus P^O$ and $P^N = P^N \cup P^R \setminus P^{NE}$, respectively. The patients in each set can be seen in the last row of Table 5.

At the beginning of week 11 (Step 2)	P^E	{1–4, 8–13, 15–23, 25–28, 30–38, 40, 42–44, 47–52, 54–55, 58, 60–86, 89–90, 92–94, 96, 99}
	P^N	{87–88, 95, 97–98, 100–110}
During week 11	P_{71}	{1, 4, 8, 10, 11, 13, 15–21, 25, 33, 47, 73, 74, 76} ∪ {107}
$P_t = \{i : R_{it} > 0, i \in P^E\}$	P_{72}	{13, 17, 18, 28, 42, 43, 44, 48, 50, 54, 58, 73, 84}
$\cup \{i : X_{it} = 1, i \in P^N\}$	P_{73}	{13, 18, 71, 73, 75} ∪ {98, 109, 110}
(Steps 3 and 5)	P_{74}	{13, 71, 73, 80, 90} ∪ {97, 98, 103, 105, 106, 109, 110}
	P_{75}	{13, 73, 90} ∪ {98, 100, 101, 104, 109, 110}
At the end of week 11 (Step 8)	P^O	{4, 11, 13, 43, 76}
	P^{NE}	{97, 98, 100, 101, 103, 104, 105, 106, 107, 109, 110}
	P^R	{111–120}
At the beginning of week 12 (Step 9)	P^E	{1–3, 8–10, 12, 15–23, 25–28, 30–38, 40, 42, 44, 47–52, 54–55, 58, 60–75, 77–86, 89–90, 92–94, 96–101, 103–107, 109–110 }
	P^N	{87–88, 95, 102, 108, 111–120}

Table 5 Numerical example - Planning

After the patients who have treatments on days 71–75 are determined, appointment scheduling problem is solved for each day. An example schedule for day 74 can be seen in Figure 4. Different colors show different nurses; patients 13, 73, 80, 90, 97, 106 are assigned to nurse 1, and patients

71, 98, 103, 105, 109, 110 are assigned to nurse 2. Patient 110 is assigned to chair 1, patients 71 and 103 are assigned to chair 2, patients 106, 97, 80, 73 are assigned to chair 3, patients 105, 109, 98 are assigned to chair 4, and patients 90, 13 are assigned to chair 5. Patient 110 with acuity level 2 (110, 2) and patient 106 with acuity level 1 (106, 1) are scheduled to arrive at time zero. Patients 90 and 103 are scheduled to arrive at time 15. They cannot be scheduled to arrive at time zero, because a nurse can start the treatment of only one patient. The completion time is 270 minutes, which is corresponds to 30 minutes of overtime.

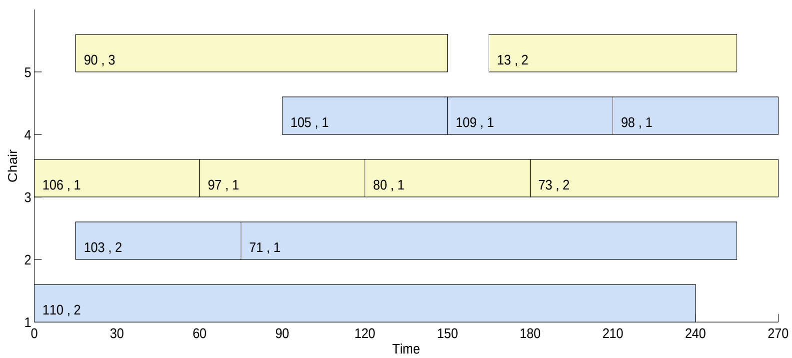


Figure 4 **Example schedule for day 74**

5. Illustration of the rolling horizon methodology

The aim of this section is to illustrate how the proposed rolling horizon approach performs. The performance measures for the planning problem are total treatment times for existing patients (P^E) and scheduled new patients (P^{NE}), total treatment delay, number of unscheduled patients, and computational times. The performance measures for the scheduling problem are the completion times found by the proposed heuristic ($ALTT$) and integer programming model (IP_3), improvement in completion time, average acuity per unit time for each nurse, number of chairs required to treat all patients and computation times. We put a time limit while solving the integer programming model IP_3 with Cplex 12.2. For the problems that cannot be solved optimally within the time limit, we present the completion time for the best feasible solution and the percentage gap between the best feasible solution and the lower bound. All computations are performed in a Unix server (SunW, UltraSPARC-IIIi) with 1503 MHz processor speed and 8 GB memory.

5.1. Problem settings

The main input to the planning problem is the patient mix. The patient mix is generated according to the expected number of new cases [2], percentage of patients receiving chemotherapy [30], and chemotherapy protocols [22]. We considered four cancer types with highest incidence rates (lung, breast, colorectal, and prostate). Table 6 shows the percentage of expected new cases over all new cases for each cancer type. The percentage of the patients receiving chemotherapy is based on the values for 2002 presented by Warren et al. [30]. Warren et al. [30] used SEER-Medicare data for 306,709 persons aged 65 and older and diagnosed with breast, lung, colorectal, or prostate cancer. When new patients are generated, the percentages in the last column are used. Thus, the probability that the patient will have lung cancer is 0.4184. The probabilities for breast, prostate and colorectal are 0.2540, 0.0717 and 0.2560, respectively.

Cancer type	Percentage of new cases [2]	Percentage of patients receiving chemotherapy [30]	Number of regimens	Average treatment duration per day (min, max)	Percentage of patients in the patient mix ($14.83 \times 35.3 + 13.13 \times 24.2 + 13.00 \times 6.9 + 10.93 \times 29.3 = 1250$)
Lung	14.83%	35.3%	11	74 (15,240)	14.83×35.3 / 1250 = 41.84%
Breast	13.13%	24.2%	39	63 (15,240)	13.13×24.2 / 1250 = 25.40%
Prostate	13.00%	6.9%	4	98 (60,180)	13.00×6.9 / 1250 = 7.17%
Colorectal	10.93%	29.3%	5	137 (75,255)	10.93×29.3 / 1250 = 25.60%

Table 6 Patient mix

Table 7 shows 59 treatment protocols that are considered in our computations. The cycle length, number of cycles, treatment days, treatment times and acuity levels for each treatment day are given. The acuity level of regimens at each treatment day is set as 1, 2, or 3, based on the number of drugs and treatment duration. As the number of drugs and treatment duration increase, the acuity level increases. For example, the second protocol has a cycle length of 28 days and the cycle is repeated 4 times. The patient has treatment on the days 1, 8, and 15 of each cycle. The treatment times are 150, 90, and 90 minutes on days 1, 8, and 15, respectively. The acuity levels are 2, 1, 1 on days 1, 8, 15, respectively. We did not consider clinical trials and other cancer types. Each protocol has equal probability of being selected.

The parameters related to clinic environment are fixed. The normal working hours are 8:00am – 4:00pm ($H_t = 480$ minutes). If the total completion time of all treatments exceeds eight hours, overtime cost is incurred. The slot length is chosen as 15 minutes and number of slots for normal working hours is 32. The clinic is assumed to be closed at weekends. The planning and scheduling problems are solved every week ($\Delta = 7$).

We considered two settings with different number of chairs, nurses and patient referrals. In the first setting, the number of chairs and nurses are set as 10 and 3, respectively. The number of patients referred to receive chemotherapy every week is ten ($|P^R| = 10$). The second setting has 20 chairs, 7 nurses and 20 new patient referrals per week. Initially, there is no patient in the system. We solve the planning problem for consecutive weeks until the system workload stabilizes.

Cancer type	Protocol	Cycle length	Number of cycles	Treatment days	Treatment times	Acuity levels
Lung	1	21	4	1, 2, 3	60, 60, 60	1, 1, 1
	2	28	4	1, 8, 15	150, 90, 90	2, 1, 1
	3	21	4	1	60	1
	4	21	4	1, 2, 3	120, 60, 60	2, 1, 1
	5	21	4	1, 2, 3	120, 60, 60	2, 1, 1
	6	28	2	1, 2, 3, 4, 5, 8	120, 60, 60, 60, 60, 60	2, 1, 1, 1, 1, 1
	7	28	4	1, 2, 3	180, 60, 60	2, 1, 1
	8	21	4	1, 8	75, 15	2, 1
	9	28	4	1, 8, 15, 22	75, 75, 15, 15	2, 1, 1, 1
	10	21	2	1	240	2
	11	21	4	1	240	2
Breast	12	21	4	1	45	1
	13	21	4	1	180	2
	14	7	12	1	60	1
	15	21	3	1	60	2
	16	21	6	1	120	2
	17	21	4	1, 4	60, 15	2, 1
	18	7	4	1	60	1
	19	21	4	1	60	1
	20	7	1	1	90	2
	21	7	12	1	30	1
	22	21	6	1	90	1
	23	21	4	1	180	2
	24	21	4	1	90	2
	25	21	6	1	105	2
	26	14	4	1	45	1
	27	14	4	1	180	1
	28	21	8	1	60	2
	29	28	4	1, 8	30, 30	1, 1
	30	21	8	1	45	1
	31	21	3	1	60	1
	32	28	6	1, 8	30, 30	1, 1
	33	28	6	1, 8	30, 30	1, 1
	34	28	6	1, 8	30, 30	1, 1
	35	7	6	1	60	1
	36	28	4	1, 8, 15	30, 30, 30	1, 1, 1
	37	21	4	1	60	1
	38	7	4	1	15	1
	39	21	4	1	75	2
	40	21	4	1	180	2
	41	21	4	1	15	1
	42	21	4	1	45	1
	43	21	4	1, 8	60, 15	2, 1
	44	28	4	1, 8, 15	30, 30, 30	1, 1, 1
	45	28	4	1, 8	60, 60	2, 2
	46	21	4	1	180	1
	47	21	4	1	240	2
	48	28	4	1, 8, 15	120, 120, 120	2, 2, 2
	49	7	4	1	15	1
	50	7	4	1	15	1
Prostate	51	21	5	1, 2, 3	180, 120, 120	3, 2, 2
	52	21	5	1, 2, 3	120, 60, 60	2, 1, 1
	53	21	4	1	60	1
	54	21	12	2	60	1
Colorectal	55	21	4	1	120	2
	56	14	12	1, 2	135, 120	3, 2
	57	14	12	1	135	3
	58	28	6	1, 2, 3, 4, 5	75, 75, 75, 75, 75	2, 2, 2, 2, 2
	59	56	3	1, 8, 15, 22, 29, 36	255, 135, 255, 135, 255, 135	3, 2, 3, 2, 3, 2

Table 7 Treatment protocols

5.2. Results

Planning problem

Table 8 shows the results for weeks 61–70 for small size problems with 10 chairs, 3 nurses, 10 referrals per week. Table 9 show the results for weeks 72–81 for large size problems with 20 chairs, 7 nurses, 20 referrals per week. The number of new patients who are waiting for their treatment to start, the total treatment time for existing patients and scheduled new patients, total treatment delay, number of unscheduled patients, and the computation times are presented.

The total treatment time of existing patients affect the number of patients that can be scheduled on a given day. For example, the total treatment time for existing patients is 2400 minutes on day 1 of week 62. No patient is assigned to that day due to unavailable capacity. Most of the treatments are assigned to days 3 and 5, which have total treatment time of 1665 and 1620 minutes for existing patients. There are weeks at which the total treatment times are low on a few days even though there are unscheduled patients (such as week 64). This is due to multiple-day treatments, where the patient requires treatment for more than one day in a week. In that case, even though there is enough capacity on one day, the patient may not be scheduled due to unavailable capacity on other days.

The average treatment delay over ten weeks is 41 for small size problems. For large size problems, the average treatment delay is 31.3. The average number of unscheduled patients is 3.2 for small size problems and 1.7 for large size problems. The decrease is due to higher number of nurses per patient (3 nurses per 10 referrals vs. 7 nurses per 20 referrals). The total treatment delay on a given week is high if there are patients in set P^N who were referred to receive chemotherapy in earlier weeks. For example, the treatment delay is 66 at week 61, because there are 8 patients in set P^N who were referred to receive chemotherapy in earlier weeks. When there is no patient from earlier weeks, then the treatment delay is high only if there is not enough capacity in earlier days of the week. For example, the treatment delay is 23 at week 62, and 8 at weeks 63 and 70. The computational times are less than a second for both small and large size problems.

Scheduling problem

After the patients are assigned to days, the scheduling problem is solved for each day of the week. Table 10 shows the results for days 420–487 (for small size problems). Table 11 shows the results of the scheduling problem for weeks 72–81 (for large size problems). The number of patients scheduled on each day (P_t), treatment completion time found by the proposed heuristic $ALTT$ and the proposed IP_3, the percentage gap between the best feasible solution and lower bound,

Week	Number of patients $\lvert P^N \rvert$	Total treatment time for existing patients (minutes) / Total treatment time for scheduled new patients (minutes)					Total treatment delay	Number of unscheduled patients	CPU time (seconds)
		Day 1	Day 2	Day 3	Day 4	Day 5			
61	18	1185 1185	1350 1005	1605 795	1800 240	1320 120	66	0	0.10
62	10	2400 0	2100 300	1665 675	2175 195	1620 660	23	0	0.06
63	10	1950 450	2400 0	2370 30	1500 375	2325 0	8	4	0.07
64	14	2265 120	1755 645	1275 675	2355 60	1680 315	27	5	0.07
65	15	1770 420	2370 0	2010 300	1560 750	2370 0	27	6	0.12
66	16	1830 570	1860 525	2370 0	2310 0	2160 240	8	6	0.08
67	16	2340 60	2385 0	1860 540	2010 390	1530 615	58	7	0.07
68	17	1605 765	990 1200	2145 255	2160 195	1740 390	114	4	0.11
69	14	1530 870	2085 300	1635 720	1860 495	1575 660	71	0	0.13
70	10	1785 570	2160 255	1725 195	2130 255	2100 0	8	0	0.05

Table 8 Planning problem results (10 chairs, 3 nurses, $\lvert P^R \rvert = 10$)

Week	Number of patients $\lvert P^N \rvert$	Total treatment time for existing patients (minutes) / Total treatment time for scheduled new patients (minutes)					Total treatment delay	Number of unscheduled patients	CPU time (seconds)
		Day 1	Day 2	Day 3	Day 4	Day 5			
72	20	4155 645	4005 630	3075 1245	2880 825	4140 645	22	0	0.11
73	20	4560 210	4755 45	4800 0	4725 75	3105 1290	36	6	0.09
74	26	4560 225	3915 855	3660 1020	2385 2265	3420 585	84	2	0.08
75	22	3660 1095	4110 675	2355 1230	3210 615	3495 315	28	0	0.08
76	20	4275 525	3510 1185	4635 180	4785 0	3285 630	22	2	0.11
77	22	3675 1065	3795 960	4485 300	3630 945	2475 180	21	2	0.08
78	22	3735 1065	4650 150	4605 195	4035 645	3210 135	23	5	0.10
79	25	2355 2325	2250 1170	3450 690	3915 150	3270 150	43	0	0.10
80	20	4290 510	4395 405	4110 675	3810 960	2700 390	24	0	0.20
81	20	3645 1110	3705 930	3675 1095	4035 330	2955 195	10	0	0.12

Table 9 Planning problem results (20 chairs, 7 nurses, $\lvert P^R \rvert = 20$)

improvement in completion time, computation time, average acuity per slot per nurse, and number of chairs required are presented.

The average number of patients scheduled per day is 21.2 for small size problems and 42.86 for large size problems. This result is expected due to the increase in number of chairs (from 10 to 20). The treatment completion time found by the proposed heuristic $ALTT$ is used as the number of slots (S) in IP_3. For example, for the $ALTT$ of day 455, the treatments are completed at the end of slot 37, which corresponds to 75 minutes overtime ($37 \times 15 - 480 = 75$). The completion time is reduced to 32 by IP_3 for day 455. For small size problems, the average improvement is in completion time is 21 minutes (1.4 slots) over 50 days. The average improvement in completion time is 17 minutes (1.12 slots) for large problems.

When IP_3 is solved, a time limit is used to reduce computational times. For small problems, the time limit is 30 minutes. For large problems, time limit is one hour. If the model cannot be solved within the time limit, the best feasible solution and the percentage gap are displayed. The percentage gap is calculated as (best feasible solution - lower bound) / best feasible solution. 47 out of 50 small size problems are solved optimally. The percentage gap is less than 3.22% for the remaining 3 problems, which cannot be solved optimally in 30 minutes. IP_3 uses the solution found by $ALTT$ as an initial feasible solution. For large problems, an optimal schedule is found for 30 days. The average percentage gap is 5.64% and ranges between 3.84% and 37.03% for 20 days at which the scheduling problem cannot be solved optimally in one hour. The average computation time is 274.84 seconds (4.6 minutes) for small problems and 2786.54 seconds (46 minutes) for large problems. Since these problems are solved once a week, the computation times are reasonable.

The average acuity level per slot per nurse is 3.47 and 3.44 for small and large problems. The average acuity level is calculated based on the slots where there is at least one patient. If the treatments are completed at the end of slot 30, the total acuity at each slot is divided by 30. The last two slots (31 and 32) are not considered in average acuity level calculations. The maximum acuity level per unit time for each nurse is 4. This means, the average nurse utilization is 86–87%. Even though the utilization U was fixed as 0.5 for the planning problem, the real utilization is more than 87% when nurse availability constraints are considered. This result shows that the capacity constraints in planning problem are approximations for the real resource utilization. The utilization parameter U should be selected carefully so that the nurses are not overloaded and planned patients can be scheduled.

After the scheduling problem is solved, the patients should be assigned to chairs. The maximum number of chairs is 8 for small problems and 19 for large problems. The planning problem was solved using 10 and 20 chairs for small and large problems, respectively. This result shows that the nursing time is the limited resource.

Week	Day	Number of patients, $\|P_t\|$	$ALTT$	IP_3					
			Completion time (slot)	Completion time (slot)	Gap (%)	Improvement (slots)	CPU time (seconds)	Average acuity per slot per nurse	Number of chairs
61	420	26	30	28	0	2	140	3.83	6
	421	24	28	26	0	2	1951	3.89	7
	422	22	34	34	0	0	103	3.34	6
	423	21	26	26	0	0	2	3.56	6
	424	13	25	25	0	0	8	2.81	6
62	427	24	34	34	0	0	468	3.43	8
	428	23	33	32	0	1	93	3.35	6
	429	18	34	33	0	1	67	3.32	6
	430	21	44	44	0	0	515	2.93	6
	431	17	27	26	0	1	35	3.74	7
63	434	26	39	37	0	2	426	3.38	6
	435	28	28	25	0	3	163	3.85	8
	436	24	31	30	0	1	86	3.64	6
	437	17	28	26	0	2	19	3.51	6
	438	18	32	31	3.22	1	1778	3.55	6
64	441	25	30	28	0	2	114	3.83	6
	442	23	34	34	0	0	92	3.33	7
	443	21	26	26	0	0	5	3.42	7
	444	23	43	42	0	1	31	3.03	6
	445	18	25	25	0	0	2	3.42	6
65	448	21	34	32	0	2	41	3.35	6
	449	23	29	27	0	2	65	3.83	7
	450	21	29	25	0	4	60	3.86	7
	451	19	35	35	0	0	15	3.39	6
	452	16	42	34	0	8	24	3.49	6
66	455	23	37	32	0	5	90	3.55	6
	456	25	30	27	0	3	85	3.85	7
	457	19	39	38	0	1	109	3.26	5
	458	19	43	41	0	2	59	3.04	6
	459	17	32	32	0	0	1	3.42	6
67	462	26	30	30	0	0	953	3.67	6
	463	25	28	26	0	2	351	3.85	8
	464	22	32	30	0	2	83	3.72	6
	465	22	37	36	2.78	1	3058	3.4	6
	466	19	31	30	0	1	61	3.47	6
68	469	24	33	30	0	3	104	3.65	6
	470	23	31	29	0	2	55	3.54	6
	471	20	33	33	0	0	5	3.28	6
	472	22	37	36	0	1	36	3.39	5
	473	19	30	29	0	1	89	3.41	6
69	476	23	33	32	0	1	65	3.53	6
	477	23	30	27	0	3	59	3.82	7
	478	21	34	32	0	2	82	3.47	6
	479	19	41	41	0	0	112	3.01	6
	480	17	34	33	0	1	48	3.2	6
70	483	25	29	27	0	2	92	3.85	6
	484	21	35	35	2.85	0	1787	3.48	6
	485	16	34	33	0	1	33	3.13	6
	486	20	44	44	0	0	20	3.01	6
	487	18	26	25	0	1	2	3.8	6
Average		**21.2**	**32.86**	**31.46**	**0.17**	**1.40**	**274.84**	**3.47**	**6.24**
Minimum		13	25	25	0	0	1	2.81	5
Maximum		28	44	44	3.22	8	3058	3.89	8

Table 10 Scheduling problem results (3 nurses)

Week	Day	Number of patients, $\|P_t\|$	*ALTT*	IP_3					
			Completion time (slot)	Completion time (slot)	Gap (%)	Improvement (slots)	CPU time (seconds)	Average acuity per slot per nurse	Number of chairs
72	497	68	26	26	23.07	0	5272	3.57	14
	498	40	29	26	3.84	3	5698	3.57	14
	499	34	29	26	0	3	775	3.51	13
	500	30	26	26	0	0	214	3.07	14
	501	32	34	34	0	0	1281	3.17	13
73	504	62	23	23	0	0	3091	3.77	19
	505	45	31	28	14.28	3	5055	3.52	14
	506	42	30	29	0	1	1060	3.41	13
	507	45	26	25	0	1	3048	3.68	15
	508	36	26	24	0	2	306	3.54	14
74	511	61	28	27	37.03	1	5110	3.53	14
	512	46	26	25	0	1	1626	3.71	14
	513	37	30	29	10.34	1	5292	3.36	14
	514	40	33	31	22.58	2	5038	3.26	13
	515	32	30	27	0	3	878	3.33	12
75	518	64	23	22	0	1	4160	3.87	18
	519	45	26	26	3.84	0	5981	3.53	14
	520	32	21	21	0	0	96	3.35	14
	521	34	24	24	0	0	34	3.16	14
	522	32	21	21	0	0	75	3.4	14
76	525	63	26	26	7.69	0	5605	3.54	14
	526	49	26	26	3.84	0	5462	3.48	14
	527	39	34	32	15.62	2	4922	3.3	14
	528	43	34	33	24.24	1	4693	3.14	13
	529	31	25	25	0	0	182	3.19	14
77	532	61	24	23	0	1	2111	3.81	15
	533	45	26	25	0	1	2696	3.62	15
	534	40	31	29	3.44	2	4845	3.43	14
	535	42	27	26	0	1	3289	3.54	15
	536	26	17	17	0	0	1	2.9	14
78	539	60	26	25	24	1	4327	3.65	15
	540	50	25	24	0	1	3506	3.7	16
	541	39	33	30	13.33	3	4609	3.36	14
	542	36	34	32	0	2	1767	3.2	11
	543	26	25	25	0	0	25	3.03	14
79	546	59	24	24	4.17	0	4737	3.7	16
	547	42	18	16	0	2	63	3.7	16
	548	34	28	27	0	1	1024	3.38	14
	549	36	27	26	0	1	577	3.4	14
	550	29	18	17	0	1	35	3.63	15
80	553	66	25	25	32	0	5372	3.56	15
	554	45	31	29	13.79	2	5175	3.45	13
	555	41	30	29	17.24	1	5747	3.4	14
	556	41	28	26	0	2	937	3.68	14
	557	26	26	26	0	0	42	2.7	14
81	560	66	22	21	0	1	327	3.8	18
	561	45	29	26	3.84	3	5667	3.45	14
	562	41	26	26	3.84	0	5561	3.48	15
	563	37	33	29	0	4	1928	3.26	13
	564	28	18	17	0	1	5	3.5	14
Average		**42.86**	**26.76**	**25.64**	**5.64**	**1.12**	**2786.54**	**3.44**	**14.30**
Minimum		26	17	16	0	0	1	2.7	11
Maximum		68	34	34	37.03	4	5981	3.87	19

Table 11 Scheduling problem results (7 nurses)

6. Conclusion and future research

In oncology clinics, the scheduling of treatments (surgery, radiotherapy, chemotherapy, etc.) for cancer patients is very important in delivering the right care at the right time. We consider planning and scheduling problems for chemotherapy patients. Chemotherapy drugs are given to patients on several days with the objective of minimizing the number of cancer cells while sparing the normal cells. Adherence to chemotherapy protocols is crucial in achieving the best health outcomes. Our aim is to achieve the best health outcomes by minimizing the treatment delays due to limited resources.

Most previous studies propose using scheduling templates/rules based on nursing or pharmacy times. The scheduling decisions are made in an ad-hoc manner according to physician and scheduler experiences and patient preferences. To the best of our knowledge, there is no study that proposes optimization methods to schedule chemotherapy treatments considering acuity levels and optimizing several objectives such as minimization of treatment delay, minimization of staff overtime and under-utilization, and maximization of staff utilization.

We proposed a two-stage approach to solve the planning and scheduling problems sequentially. Integer programming models are proposed to solve these problems. A rolling horizon approach is used to schedule new patients who are referred to receive chemotherapy. A heuristic and an integer programming model are proposed to reduce the computation times for the scheduling problem. The computational result show that the planning and scheduling problems can be solved in reasonable times. The proposed planning and scheduling models can be used as a decision making tool in determining the optimal staffing levels.

The proposed methods have a few implementation challenges. The acuity levels for each treatment should be estimated based on nurse experience and/or time studies where nursing times for each treatment are collected. The impact of delays on patient's health should be quantified. The parameters in the planning problem should be set carefully so that everyone can be scheduled without overloading nurses.

As future research, multiple stages of the treatment process such as registration, vitals, labs, pharmacy, oncologist visits should be considered while scheduling the patients. In a real clinic environment, there are many uncertainties such as delays in getting lab results, cancellations, add-on patients, etc. that affect the daily performance. Delays increase the patient waiting times and affect the clinic flow. Most of the cancellations occur on the same day after the lab results are performed and the patient is seen by the oncologist. Add-ons might occur within the last few days. The schedule should be revised in order to accommodate as many patients as possible with the objective of minimizing the treatment delays, patient waiting times and staff over time. The variability in treatment times makes the rescheduling process very complicated. Rescheduling methods should be proposed to cope with uncertainties.

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