




A bi-level multi-follower optimization model for R&D project portfolio: an application to a pharmaceutical holding company

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Abstract

The need for a study of project portfolio optimization in pharmaceutical R&D has become all the more urgent with the outbreak of COVID-19. This study examines a new model for optimizing R&D project portfolios under a decentralized decision-making structure in a pharmaceutical holding company. Specifically, two levels of decision makers hierarchically decide on budget allocation and project portfolio selection-scheduling to maximize their profit, and we formulate the problem as a bi-level multi-follower mixed-integer optimization model. At the upper level, the investment company has complete knowledge of the subsidiaries' response, acts first, and decides on the best budget allocation. At the lower level, each subsidiary responds to the allocated budget and decides on its portfolio scheduling. Since the lower level represents several mixed-integer programming problems, solving the resulting bi-level model is challenging. Therefore, we propose an efficient hybrid solution approach based on parametric optimization and convert the bi-level model into a single-level mixed-integer model. To validate it, we solve a case and discuss the optimal strategy of each actor. The experimental results show that the planned project portfolio for each subsidiary of the holding company is drastically affected by the allocated budget and its decisions.

Keywords R&D project portfolio · New product development · Budget allocation · Bi-level multi-follower modeling · Pharmaceutical holding company

1 Introduction

In today's ever-changing competitive world, R&D plays a critical role in the success of organizations. Managing and optimizing the portfolio of projects in various industries is a critical factor that significantly affects the companies' activities and their success in fulfilling

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their missions. Given the costly projects, limited resources, high-risk phases, and unique supply requirements, the pharmaceutical industry presents the most complex problem in terms of optimizing R&D planning. Statistics show that the percentage of pharmaceutical R&D projects that reach the final stage is meager (Gemici-Ozkan et al., 2010). However, R&D in the industry is necessary because it has a critical impact on human and public health through the development of new drugs and vaccines, the production of generic drugs, and the design of the specific supply chain associated with them (Ahmadi et al., 2018). The trend in R&D spending in the United States shows skyrocketing growth from 1980 (Fig. 1), when the allocated amount was two billion dollars, to eighty-three billion dollars in 2019. According to the U.S. Food and Drug Administration (FDA) reports, pharmaceutical companies have invested more than half a trillion dollars in R&D over the past decade, and more than 350 approved new drugs have been launched (Benmelech et al., 2021). The Coronavirus pandemic of 2020–2021 has spurred many top holdings to develop vaccines and produce related drugs to stop the spread of COVID-19. In addition to private sector investment in R&D, the U.S. federal government has supported the private sector in developing vaccines and effective medicines to combat the pandemic and related diseases (Snyder et al., 2020). A popular project portfolio planning approach in a pharmaceutical holding is through a centralized system based on market demand. However, there are problems with budget allocation between subsidiaries and the preferences and competencies of subsidiaries. For business owners in holding companies, budget allocation to subsidiaries and the utilization of the subsidiaries' competencies have become more important. It becomes even more challenging when different entities make the decisions about budgeting and selection-scheduling.

According to the above explanation, project portfolio planning in a holding is traditionally managed in a centralized manner. In other words, decision-making authority is concentrated in a single office, with a single decision maker making both budgeting and selection-scheduling decisions. However, such a system needs to be rethought under the new planning configuration. Today, the project portfolio in leading holding companies is managed by a decentralized system in which the investment company focuses on budgeting. The subsidiaries, on the other hand, take care of project selection and scheduling of projects. In such a decentralized system, the decision-making process involves two levels of decision makers. Moreover, each level makes a subset of decisions to optimize its own (local) objective while influencing and

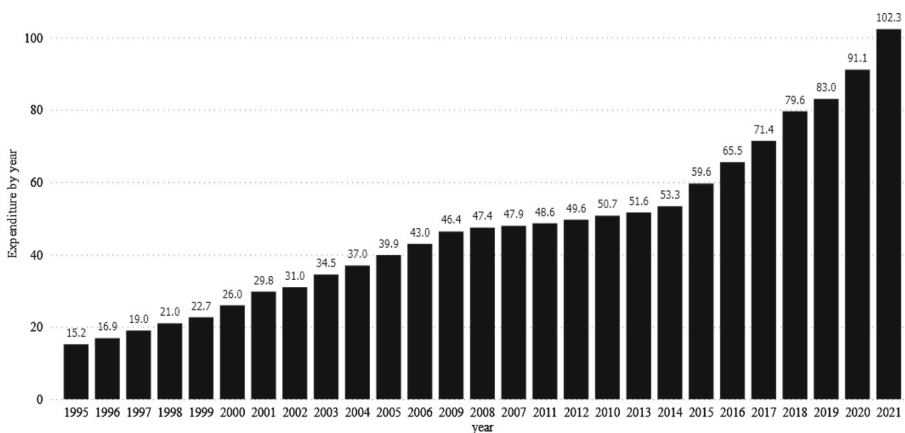


Fig. 1 Total U.S. pharmaceutical industry R&D expenditure from 1995 to 2021 (in billion U.S. dollars)

being influenced by the decisions of the other level. For example, in a real-world case, an investment company that is part of Pfizer, a well-known pharmaceutical holding company, set \$600 million in 2018 to be shared among the holding company's subsidiaries to access internal Pfizer expertise in transformative therapeutics.

This paper addresses the project portfolio planning problem in a pharmaceutical holding under a decentralized decision-making structure. The main objectives of project portfolio management in the holding company are optimized budget allocation and the lucrative selection and scheduling of projects in each subsidiary. However, it is not optimal to plan a project portfolio in such a centralized way without considering the subsidiaries' preferences and competencies. Therefore, to meet the requirements of the holding company, it is important to gain insight into the budget allocation between subsidiaries and the project portfolio selection-scheduling in each subsidiary in relation to its area of expertise. In this way, appropriate budget allocation and profitable project portfolio planning in each subsidiary become an inevitable part of project portfolio management in a holding company. Following traditional research, (Hesarsorkh et al., 2021) studied a project portfolio optimization problem in a pharmaceutical company with a centralized decision-making structure. In their study, the company is considered a development company, and the initial investment is defined as a parameter, as well as external resources, in the budget constraint optimization model. However, subsidiaries are unable to play a significant role due to this financing approach. The competence of some subsidiaries may be neglected, while others may be overburdened and suffer losses. However, these challenges become even more complicated when budget allocation and selection-scheduling decisions are decentralized among different levels. Despite the importance of "decentralization" in project portfolio management, the question of how to optimize the conflicting interests of decision makers for project portfolio planning in a hierarchical, game-based situation still needs to be supported by portfolio management professionals and researchers.

To address these challenges, we propose a bi-level multi-follower project portfolio planning problem in a pharmaceutical holding company, where the investment company's problem belongs to the upper-level optimization model, and the subsidiaries' problems belong to the lower level. In this paper, we consider an investment company responsible for allocating budget to subsidiaries in a holding structure and providing them with the budget to select and plan their own project portfolio within a predefined time period. A management system determines the R&D budget allocated for planning development projects in a holding company. Thus, an optimal portfolio of projects should be selected and scheduled. However, centralized decision-making may result in a holding company's project portfolio not matching the preferences of individual subsidiaries due to neglected competencies. The investment company, which is in charge, makes budget allocation decisions to maximize the holding company's profit. At the inner level, with the subsidiaries acting as followers, each subsidiary makes the selection-scheduling decisions to maximize its own profit, also taking into account the budget allocated by the investment company. Along with the allocated budget, each subsidiary has a credit budget from outside resources, which can be used to create a profitable portfolio based on the company's competencies. The decisions of each level affect and are affected by the decisions of the other level. For instance, the selection and execution of more projects favor the investment company as it means a higher profit for the holding company. However, it may not meet the objectives of some subsidiaries seeking a profitable portfolio based on their competencies. Hence, ignoring the stated game may result in losses for some subsidiaries and missed opportunities for the holding company.

In this context, our proposed bi-level multi-follower model aims to find the preferred budget allocation of the investment company (leader) based on the best portfolio selection-scheduling of each subsidiary (follower), to maximize the benefit of the holding company, while ensuring that each subsidiary meets its highest objective amount. More importantly, our framework allows us to determine the best budget allocation among subsidiaries in a holding environment while considering the optimal project selection configuration and scheduling of the selected projects by each subsidiary.

Finally, considering review papers such as those (Vahid Mohagheghi et al., 2019; Saiz et al., 2022), optimizing a game-based project portfolio problem with multiple complex subproblems such as budget allocation and multiple project portfolio selection-scheduling (PPSS) with realistic features such as the limited available budget for allocation, the credit limit for each follower, the limited number of resources, and interdependence among projects, we propose a mixed-integer bi-level multi-follower model that is very difficult to solve. Due to their NP-hard nature, bi-level optimization models have posed a challenge to researchers for many years (Sinha et al., 2018). This becomes even more challenging when the model consists of integer variables since it would be impossible to apply well-known approaches such as KKT to such a model. Therefore, this study presents a hybrid solution method for solving the programmed bi-level multi-follower model, which addresses the specific characteristics of this model, including its multi-follower nature and binary variables (Dempe & Kue, 2017). Our proposed solution method involves reformulation and parametric optimization. The parametric optimization model of each follower is solved using the B&B algorithm in our proposed solution method. Based on the solutions obtained from each follower's model, the proposed bi-level model is converted into a single-level mixed integer model and solved based on classic algorithms. In addition, the proposed mathematical programming has been examined using a professional dataset for a pharmaceutical holding company. These are the results of this study, which hopefully contribute to the development of the relevant literature.

The rest of the paper is organized as follows. Section 2 reviews the related literature. In Sect. 3, we describe the structure of the holding company and formulate the proposed bi-level multi-follower problem. In Sect. 4, we develop and illustrate the solution approach. In Sect. 5, we turn to numerical experiments and applications. Finally, in Sect. 6, we conclude and suggest ideas for future studies.

2 Literature review

Budgeting, selection, and scheduling, as three strategic and operational functions, play a key role in project portfolio planning, the optimization of which can significantly improve management performance. Recently, the problem of project portfolio selection-scheduling (PPSS) has received considerable attention in both academic research and industry practice. However, decentralized decision-making in project portfolio planning is rarely discussed in the literature on the subject. This section reviews the existing literature on our framework. The relevant studies are presented and classified from different points of view.

From the review of relevant literature, it can be concluded that studies on project portfolio planning have been classified into five groups: benefit measurement methods, mathematical optimization models, cognitive emulation approaches, heuristic methods, and simulation (Vahid Mohagheghi et al., 2019).

Regarding the category of mathematical optimization to which the present study contributes, the majority of existing works have focused on simplified and traditional models

that involve the selection of projects considering the return on investment, budget constraint, resource allocation (Carazo et al., 2010; Farid et al., 2021; Flidner & Liesiö, 2016; Rogers et al., 2002; Wang & Hwang, 2007) and project interactions (Alvarez-Garc & Fernández-Castro, 2018; Arratia et al., 2016). Hierarchical optimization models have also been gradually developed, in which the selection and scheduling of projects are hierarchical (Hans et al., 2007; Vazhayil & Balasubramanian, 2012). The challenges of suboptimality and the infeasibility of hierarchical models have encouraged researchers to configure integrated optimization models that consider scheduling as an integral part of the project selection process. However, a few researchers have developed integrated optimization models with simultaneous project selection and scheduling. The addition of scheduling as an essential concept to the mathematical models of project portfolio planning has changed the structure of the models due to the feasible regions and objective functions involved. Table 1 provides an overview of the existing literature on integrated optimization models. Different criteria are used to describe and classify the relevant studies.

From Table 1, we can infer that the majority of scholars studying PPSS have focused on traditional optimization models by considering various factors in their studies, such as project task planning (Rafiee et al., 2014), project interdependencies (Kumar et al., 2018), success risk (Mohagheghi et al., 2017), and the vague nature of the problem (Pérez et al., 2018). In particular, very few works on PPSS have addressed some rather complicated planning configurations, such as multistage projects (Hassanzadeh et al., 2014; Hesarsorkh et al., 2021) and dynamic budgeting (Shafahi & Haghani, 2018), where the allocated budget can be saved and carried over to subsequent periods. Moreover, none of the PPSS studies on budget allocation mentioned above has dealt with a real-world investment scenario such as that of holding companies.

The importance of pharmaceutical PPSS and the essence of this concept have been explained succinctly and summarized by (Antonišević, 2015). As shown in Table 1, few works in mathematical programming have addressed the integrated problem in the pharmaceutical industry. (Schmidt & Grossmann, 1996) The first related work developed a MILP model for testing task sequencing. (Jain & Grossmann, 1999) extended the previous study by considering resource constraints. (Colvin & Maravelias, 2008) developed a multistage stochastic mixed-integer optimization model with endogenous uncertainty in clinical trials. Another paper (Colvin & Maravelias, 2009) addressed outsourcing. (George & Farid, 2008) proposed a multi-objective optimization model considering expected NPV and project interdependencies, which were both modeled in their study. (Rogers et al., 2002) extended stochastic programming to optimize the project selection model using real options theory. They also implemented their model on a case. (Wang & Hwang, 2007) studied a mixed-integer optimization model with binary variables. They also used a fuzzy set approach to deal with uncertainty in the pharmaceutical industry. (Hassanzadeh et al., 2014) is one of the valuable integrated works that propose a mixed-integer mathematical optimization model for project selection and scheduling. They drew on the robust optimization theory to overcome uncertainty. (Hesarsorkh et al., 2021), recent work in the field of project portfolio management proposed a comprehensive, robust optimization model for project selection and scheduling, addressing outsourcing.

All of the works focused on the central decisions of PPSS. However, in many real-world situations, budgeting decisions for the R&D project portfolio and selection-scheduling decisions are made by different entities as part of a decentralized decision-making process. Bi-level optimization, as an analytical tool for hierarchical decentralized decision-making problems, still needs to be analyzed and supported by PPSS researchers; (Aghababaei et al., 2021) in which the authors proposed a bi-level optimization model for managing scarce drug

Table 1 Summary of related PPSS studies

Author(s)	Decentralized setting	Pharmaceutical industry	Objective		Job scheduling	Project Scheduling	Project interdependencies	Investment decisions	Multi stage projects	New solution method	Other features
			Profit	Risk							
(Ghasemzadeh et al., 1999)	-	-	✓	-	-	✓	-	-	-	-	-
Sun and Ma, (2005)	-	-	✓	-	-	✓	-	-	-	-	Case study
(Zuluaga et al., 2007)	-	-	✓	-	-	✓	✓	✓	-	-	Project time frame
Solak et al., (2010)	-	-	✓	-	-	✓	✓	✓	✓	Exact	-
Hassanzadeh et al., (2012)	-	✓	✓	-	-	✓	-	-	✓	-	Fuzzy programming
Rafiee et al., (2014)	-	-	✓	-	✓	✓	-	-	✓	Heuristic	Stochastic optimization
Hassanzadeh et al., (2014)	-	✓	✓	-	-	✓	✓	✓	✓	-	Robust optimization
Montajabiha et al., (2017)	-	✓	✓	-	✓	✓	-	-	✓	Exact	Robust optimization
Shariatmadari et al., (2017)	-	-	✓	✓	✓	✓	-	-	-	Heuristic	GSA algorithm

Table 1 (continued)

Author(s)	Decentralized setting	Pharmaceutical industry	Objective		Job scheduling	Project Scheduling	Project interdependencies	Investment decisions	Multi stage projects	New solution method	Other features
			Profit	Cost Risk							
Mohagheghi et al., (2017)	-	-	✓	-	✓	✓	✓	✓	-	-	Type-2 fuzzy optimization
Pérez et al., (2018)	-	-	✓	-	✓	✓	-	-	-	Heuristic	Fuzzy constraints
Kumar et al., (2018)	-	-	✓	-	✓	✓	-	-	-	Meta heuristic	Hybrid solution method
Amirian and Sahraeian, (2018)	-	-	✓	✓	✓	-	-	-	-	Heuristic	Fuzzy goal programming
Zhang et al., (2019)	-	-	✓	-	✓	✓	-	-	-	Meta heuristic	Fuzzy programming
Hesarsorkh et al., (2021)	-	✓	✓	-	✓	✓	✓	✓	✓	-	Robust optimization
Ranjbar et al., (2021)	-	-	✓	✓	✓	✓	-	-	-	-	Multi-mode projects
Present study	✓	✓	✓	-	✓	✓	✓	✓	✓	Heuristic	Multi-level model

supply and rationing in emergency situations. The model didn't investigate project selection. (Ma, 2016) proposed a bi-level project portfolio selection model in a project portfolio management environment but studied a very simple and unrealistic system in terms of marketing constraints. Moreover, it used a metaheuristic algorithm to solve the leader–follower optimization model.

2.1 Summing up the literature

We have reviewed almost all major works on project portfolio planning and related optimization models. We have also reviewed key works on project portfolio management for the pharmaceutical industry.

In this paper, we extend a new comprehensive optimization model that adds the following features to the previous studies on the project portfolio planning problem:

- This work, with regard to new product development and R&D project portfolio optimization, presents a bi-level multi-follower mix integer optimization model for project portfolio optimization.
- As a novelty of the model, the existing Stackelberg game between the investment and operational sides of a holding company is considered for the defined problem.
- Inner level of the bi-level programming consists of multi followers with mix-integer programming.
- The model was applied to a pharmaceutical holding company whose market share and public health depend heavily on R&D.
- An efficient solution approach is proposed for the resulting bi-level multi-follower mixed-integer project portfolio optimization model, which belongs to a class of models known to be difficult to solve.

In terms of modeling, we model the budgeting problem with mixed integer programming as the investment company's problem (leader's problem). As for the subsidiaries' problem, we adopt realistic assumptions for PPSS as we consider credit from external resources for each subsidiary, technical dependencies between projects, and limited technical resources. We adopted our programming with the proposed solution approach by establishing a budget bound for each follower's model in order to formulate parametric mixed integer models, and by using a binary variable in the leader's problem to select the optimal region from calculated regions for each follower's model. To our knowledge, and as we demonstrated in the literature review section, this is the first work on project portfolio planning that integrates all these features into the same bi-level model. We address the complexity of a bi-level multi-follower with mixed-integer models at the lower level in terms of solution and computation. It is well known that solving such a model is challenging. Due to the NP-hard nature of PPSS, we use an efficient solution approach based on parametric optimization and recasting the model into a single-level mixed-integer optimization model.

3 Bi-level multi-follower programming

In the literature, bi-level programming has been applied to the study of the Stackelberg game between determiners in different domains, such as supply chain management and resource allocation. There are two levels in this type of model, namely the upper level of the leader(s) and the inner level of the follower(s) that make decisions in a hierarchical and decentralized manner. This type of programming was first introduced to economic game theory literature

by Heinrich Stackelberg. Upper-level decision makers (leaders) initiate the first action to optimize their objectives. Likewise, the outcome of each solution or decision they make is dependent upon the response of lower-level entities (followers), who are also working to achieve their objectives.

Multilevel programming is also an extended form of bi-level programming. Programming deals with decisions made in hierarchical and decentralized processes. Many large-scale optimization problems and decision-making processes faced by public and private organizations are decentralized and hierarchical, with multiple decision makers at each level, referred to as multilevel programming in the bi-level programming literature. According to a review (Sinha et al., 2018), different bi-level optimization models have been studied for different problems. However, there is still a gap in bi-level optimization models in project portfolio management.

In this research, a special type of bi-level programming was used to build an appropriate model for investment and selecting-scheduling decisions of project portfolios in holding companies. The problem included a leader at the upper level and decision makers with multiple followers at the inner level. The followers at the lower level have binary variables. Therefore, the proposed model was categorized as a mixed-integer, bi-level, linear mathematical programming with multiple followers. The objective function of the proposed model was also upper level and searched for the best holding project portfolio with maximum profit depending on the lower-level responses. In addition, each follower pursued its own target and was empowered to select and plan its potential projects.

3.1 Structure of the problem

In the programmed model, the entities of project portfolio management consist of two types of decision-makers, including the upper level (leader) and the lower level (followers). The followers are considered as subsidiaries of the holding company (leader), and the investment company as the leader can influence their decisions through strategic decisions that should be considered by the subsidiaries (Johnson et al., 2017). Therefore, the strategic decisions of the holding company are made at the upper level by the leader company. However, the subsidiaries make the technical and operational decisions, and each subsidiary has the opportunity to pave the way for its own objectives. Thus, both levels are involved in a PPSS problem. An investment company makes budget decisions (the most strategic decisions) and tries to maximize the profit of the whole holding company. On the other hand, each subsidiary focuses on its own profit without considering other subsidiaries or the objectives of the higher level. In a PPSS model, subsidiaries make selection and scheduling decisions for their specific area, such as production potential and development project execution. They also have the authority to use other resources (e.g., loans) as needed to achieve more worthwhile goals. The structure is depicted in Fig. 2.

3.2 Suppositions and clarifications

- The holding company consists of an investment company and several subsidiaries.
- The total share of each subsidiary has been divided between the holding company and the company's shareholders.
- The holding company sets a budget for R&D and intends to invest it in the subsidiaries to develop new products and execute development projects.
- The role of the investment company is to allocate the R&D budget to the subsidiaries.

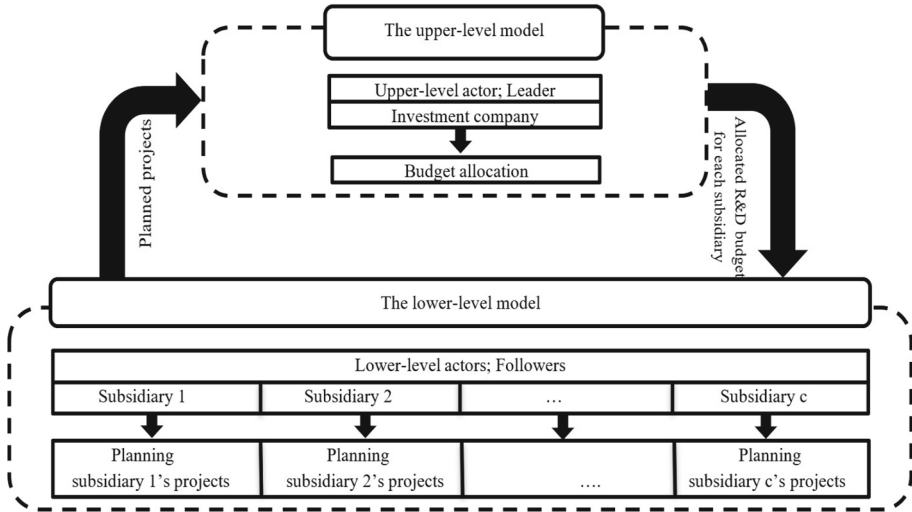


Fig. 2 Decentralized decision-making structure for PPSS in a holding company

- The subsidiaries carry out new product manufacturing and development projects in their respective fields.
- The leader allocates the R&D budget to each follower in the first period of the planning horizon, to be handled by the follower during the horizon.
- Each subsidiary has a pool of projects and selection-scheduling decisions made by it.
- The required budget of each subsidiary is provided by the allocated budget of the investment company and by loans from external sources. The borrowed budget increases by a certain percentage per period.
- Each project included in the pool of each subsidiary has multiple stages (phases) to complete.
- Each stage has multiple periods to complete.
- Funds for each phase of project completion are allocated in the first period of the planning of the phase (e.g., after completion of the previous phase).
- Revenue from a completed project is divided between the holding company and the related subsidiary according to each side's share of the company's total share.
- The additional cash in each company's account is increased by a fixed rate per period.
- The amount of loan amount is limited in each period for each subsidiary, and the maximum amount of loan is set for each subsidiary.
- The cost of completing stages that are part of a project increases at a fixed rate if the start is delayed, and the earning value of the project decreases exponentially if the project is postponed.
- Different types of renewable resources are needed to complete the project phases, and their availability is limited in each subsidiary (Tables 2, 3 and 4).

$$Max Z = I_{T+1} \tag{1}$$

Subject to:

$$I_t = T B_t - \sum_{c \in C} B_{t,c}, \quad t = 1. \tag{2}$$

Table 2 Indices of sets

I	Set of projects in each company, represented by i or g
C	Set of subsidiaries, represented by c
M	Set of resource types in each company, represented by m
K	Set of stages, represented by k
T	Set of periods, represented by t or j

Table 3 Parameters of the Bi-level model

TB	Total amount of budget planned to inject into followers and investment in R&D projects
N_c	Number of potential projects in company c
k_i	Duration of project i in company c in terms of stages or periods (project life)
es_{ic}	Early start time of project i in company c
ts_{ic}	Tardy start time of project i in company c
c_{itc}^k	Cost of performing k th stage of project i in period t that could be change by start time of project i
$Inc_{ic}^{k_i+1,t}$	Estimated income of project i in company c if performed at the beginning of period t ($k \leq k_i$)
$re_{im,c}^k$	Amount of resource type m required to complete the k th stage of project i in company c
r_t	Interest rate upon a period
δ	Loan repayment rate upon a period; strictly positive
α_c	Percentage of total share belonging to company c
LL_c	Loan (liability) limit for company c
RE_{im}^c	The amount of available resource type m that can be consume in period t in company c
T	Length of planning span in periods
Δ_{ip}^c	Split between two projects i and g that arises from interdependency
Set_c^M	Set of mandatory projects that must be selected in planning horizon
Set_c^O	Set of ongoing projects that must be selected in first period of planning horizon

Table 4 Decision variables of the Bi-level model

<i>Upper-level decision variables</i>	
$B_{t,c}$	Amount of budget allocated to company c at the beginning of planning period
I_t	Amount of extra cash belonging to the holding company at the beginning of period t
<i>Inner-level decision variables</i>	
x_{it}^c	Binary variable, being equal to 1 if project i initiated at the beginning of period t in company c , and 0, otherwise
I_{tc}	Amount of extra cash in the account of company c at the beginning of period t
L_{tc}	Borrowing amount at the beginning of period t in company c
θ_{tc}	Usage of allocated budget in each period in subsidiary c

$$I_t \leq \sum_{c \in C} \sum_{i \in I} \sum_{j=es_i}^{t-k_i} (1 - \alpha_c) Inc_{i,c}^{k_i+1,t} x_{i,j}^c + I_{t-1}(1 + r), \quad t = 2, \dots, T. \tag{3}$$

$$\sum_{c \in C} B_{t,c} \leq TB, \quad t = 1 \tag{4}$$

Based on the traditional form of bi-level programming, the upper-level objective function and constraints are defined in Eqs. (1–4). Equation (1) is the objective function of the problem and the leader; it considers the maximum amount of cash in the leader’s account at the end of the planning horizon. Equation (2) states that the amount of cash in the leader’s account in the first period is equal to the remaining amount of the total planned R&D budget after allocation to the subsidiaries. It illustrates the balance of cash in the first period. Equation (3) defines the cash balance for all other periods. In it, the amount of cash in each period is determined from the income of completed projects and inflated amount with interest rate from previous period. Equation (4) guarantees that sum of the budget allocated to subsidiaries is less than the total R&D budget planned to inject to subsidiaries.

The inner level of programming consists of |C| followers with respect to the holding company. Each subsidiary schedules its project portfolio using a mathematical PPSS model with available sources.

$$Max Z_c = I_{T+1,c} - L_{T+1,c}, \quad \forall c \in C \tag{5}$$

Equation (5) represents the objective function of each follower. In order to achieve the objective, the function maximizes the extra cash available in the account after covering the liabilities.

Subject to:

$$\sum_{i \in I} \sum_{j=\max\{es_i, t-k_i+1\}}^{\min\{t, ts_i\}} c_{it,c}^{t-j+1} x_{ij}^c + I_{t,c} + L_{t-1,c}(1 + \delta) \leq \dots \tag{6}$$

$$\sum_{i \in I} \sum_{j=es_i}^{t-k_i} \alpha_c Inc_{i,c}^{k_i+1,t} x_{i,j}^c + I_{t-1,c}(1 + r) + L_{t,c} + \theta_{t,c}, \quad \forall c \in C \& t = 1 \dots T$$

Constraint (6) shows the balance of cash in each period. It establishes the cash balance at the end of the period. The cash increases through the budget allocated by the investment company (leader), loans, interest earned on cash saved from previous periods, and income from completed projects. The repayment of the borrowed amount at borrowing rate δ should be made in time period j , which is spent on the initiated phases of the project. Parameter α is defined as the percentage of the total share in each subsidiary that leads to the distribution of revenues from the completed project.

$$\sum_{j=es_i}^{ts_i} x_{ij}^c \leq 1, \quad \forall c \in C \tag{7}$$

Constraint (7) guarantees that a project in each subsidiary portfolio can be selected once during the planning horizon.

$$\sum_{i \in I} \sum_{j=\max\{es_i, t-k_i+1\}}^{\min\{t, ts_i\}} re_{im,c}^{t-j+1} x_{ij}^t \leq RE_{im}^c, \quad \forall c \in C \& t = 1, \dots, T \tag{8}$$

Constraint (8) guarantees that the maximum available quantity of each renewable resource (i.e., specialists and laboratories) in each period cannot be less than its used quantity.

$$x_{pt}^c \leq \sum_{j=\max\{es_i\}}^{\min\{ts_i, t-k_i-\Delta_{ig}\}} x_{ij}^c, \forall c \in C \& t = 1, \dots, T \tag{9}$$

Constraint (9) shows interdependencies between projects i and g , and it guarantees that project i cannot begin until project g is selected and scheduled. This constraint defines a complementary relationship between the projects and technical dependencies between them.

$$L_t^c \leq LL_c, \forall c \in C \& t = 1, \dots, T \tag{10}$$

Constraint (10) guarantees that the cash borrowed in each period does not exceed the borrowing limit in each period for each subsidiary.

$$\sum_{t=1}^T \theta_{tc} \leq B_{1,c}, \forall c \in C \& t = 1, \dots, T \tag{11}$$

Constraint (11) guarantees that the use of the budget does not exceed the total budget allocated to each subsidiary by the leader.

$$\sum_{j=es}^{ts} x_{ij}^c = 1, \forall c \in C \& i \in Set_c^M \tag{12}$$

Constraint (12) guarantees that mandatory projects are selected and scheduled during the planning horizon.

$$x_{i1}^c = 1, \forall c \in C \& i \in Set_c^O \tag{13}$$

Constraint (13) guarantees that ongoing projects are selected to continue in the first period.

$$x_{ij}^c \in \{0, 1\} \ i = 1 \dots N_c \& j = es \dots ts \tag{14}$$

$$I_{t,c}, L_{t,c}, \theta_{t,c} \geq 0 \tag{15}$$

$$I_t, B_{t,c} \geq 0 \tag{16}$$

$$0 \leq B_{1,c} \leq TB \tag{17}$$

Constraints (14) and (15) guarantee the non-negativity of the decision variables and the range of each follower. Constraint (16) guarantees the non-negativity of the leader’s decision variables. Constraint (17) specifies that the allocated budget for each subsidiary is bounded between zero and the total budget. Constraint (17) is a logical constraint and established in the model because we want to use the parametric approach.

4 Solution approach

Multilevel programming is a class of mathematical programming used to optimize decentralized decision-making problems. Bi-level programming is a type of multilevel programming that refers to mathematical optimization models that work with a hierarchical structure and involve two decision makers: a leader and a follower (Vicente and Calamai 1994). This type

of programming is applied to various practical problems, such as in economics (Ding et al., 2021), supply chain management (Cao et al., 2021), logistics (Mirzaei et al., 2021), and revenue management (Dempe & Kue, 2017). Each level in bi-level programming can have more than one decision-maker. In other words, a problem with multiple leaders or multiple followers can be programmed using this type of programming technique (Bard, 2013; Sinha et al., 2018). Few studies in the literature have addressed multilevel programming.

Several studies have proposed solutions for linear bi-level mathematical models. However, mixed-integer bi-level programming is NP-hard and challenging to solve, especially when the inner level contains discrete variables (Sinha et al., 2018). However, the methods proposed in studies to deal with mixed-integer bi-level problems with multiple followers are sparse. A number of studies have developed an algorithm for solving mixed-integer bi-level programming with integer variables at the inner level (Cao et al., 2021; Dempe & Kue, 2017; Köppe et al., 2010; Liu et al., 2021; Mitsos et al., 2008; Xu & Wang, 2014). As far as we know, a bi-level multi-follower problem with integer variables in the inner levels needs to be transformed into a bi-level model with one follower to fit the existing solutions. Another approach is to reformulate the problem into a single-level problem and use classical methods to find a solution.

In the proposed bi-level mixed integer programming (BLMIP) model, since the inner level consisted of multiple followers, and the problems were formulated as MILP models, it was difficult to solve them. Therefore, a novel solution approach was used in this study. Given the nature of bi-level programming, it is known that the upper-level variables affect the inner-level variables. The idea is to reformulate bi-level linear programming as a single-level model through parametric programming (Sinha et al., 2018).

Parametric programming is a type of mathematical optimization in which a problem is solved as a function of one or more parameters using a piecewise linear solution (Gal & Greenberg, 2012). In this concept, mathematical models consisting of integer variables (Avraimidou & Pistikopoulos, 2019; Dua & Pistikopoulos, 2000) are also studied. (Dua & Pistikopoulos, 2000) introduced a branch-and-bound (B&B) algorithm to solve a linear multiparametric mathematical model with binary variables, where the parameters are bounded by lower and upper bounds that exist on the right-hand side (RHS) of the constraints. (Oberdieck et al., 2014) expanded the B&B algorithm where the coefficients of the objective functions can also vary between lower and upper bounds. As mentioned earlier, the upper-level variables affect the inner-level problems. Accordingly, each inner level problem (here, the problem of each subsidiary) is transformed into a multiparametric model and can be solved using the algorithm proposed by (Oberdieck et al., 2014). Therefore, we adapted the algorithm to our problem, and the set Ξ is the assigned parameter space with a lower bound of zero and an upper bound containing the total R&D budget to be allocated to the subsidiaries (constraint 17). The optimal solution to problems 5–16 for each subsidiary is a piecewise affine function in Ξ , for more detail see (Oberdieck et al., 2014).

In the bi-level multi-follower model proposed in this paper, the leader decides on budget allocation. The leader determines the allocated budget that each follower in the PPSS model can use to select and schedule its own portfolio. As mentioned earlier, the allocated budget can be used as the right-hand side of Constraint (11). A parameter with a lower bound of zero and an upper bound defined as the total budget was decided to be allocated to subsidiaries [constraint (17)]. Accordingly, each follower's problem is a specific version of a parametric mixed-integer linear programming (P-MILP). Figure 3 shows the flowchart of the branch-and-bound algorithm for the parametric mixed-integer linear programming (P-MILP) optimization model. Applying the B&B algorithm yields optimal solutions in the feasible

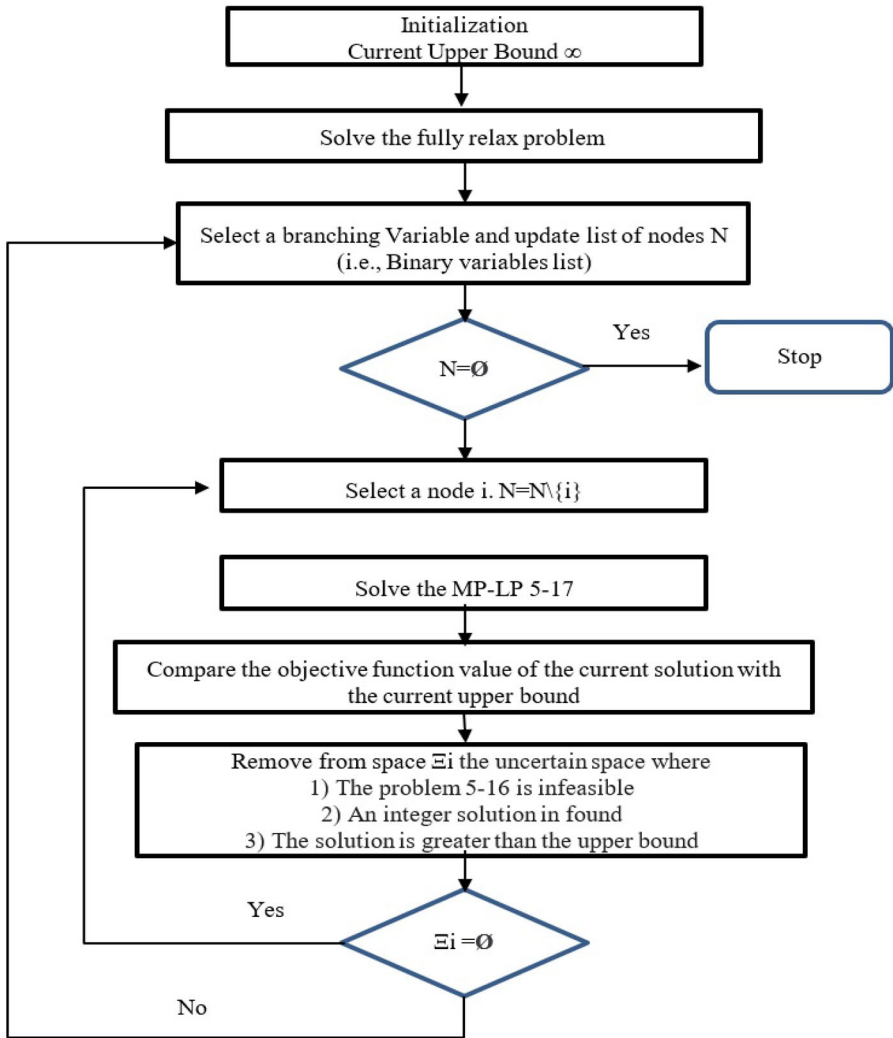


Fig. 3 The customized Multi-parametric Mix-integer Linear programming (MP-MILP) solution algorithm by (Oberdieck et al., 2014)

space of upper-level variables with multiple critical regions. For clarification, the supposed parametric problem solution for follower q is presented in rows 1 and 2 of Table 5.

It is clear that the allocated budget for each follower (e.g., follower q in Table 5) belongs to one region among the calculated regions for the follower. Thus, only one region needs to be selected and the optimal solution of the selected region is used as a parameter for the leader’s problem. It is also obvious that the allocated budget is the lower bound of the selected region, considering the interest rate on the remaining cash in the investment company’s account. In other words, allocating more than the lower bound does not improve the leader’s objective function value. Accordingly, it does not affect the optimal solution. Therefore, model 1–17

Table 5 A supposed calculated solution for follower q parametric problem

Calculated regions	Scheduled projects	γ_{pq}	Value of this region for the holding company (at the end of the planning horizon)	Allocated budget if the region is selected
$0 \leq B_{1,q} < b_1$	x_{it}^q, \dots	1 if region 1 selected, 0 otherwise	$(1 - \alpha_c)(1 + r)^{T-t-k_i+1} (nc_{i,q}^{t+k_i} x_{i,t}^q) + \dots$	0
$b_1 \leq B_{1,q} < b_2$	$x_{i't}^q, \dots$	1 if region 2 selected, 0 otherwise	$(1 - \alpha_c)(1 + r)^{T-t-k_{i'}+1} (nc_{i',q}^{t+k_{i'}} x_{i',t}^q) + \dots$	b_1
$b_n \leq B_{1,q} < TB$	$x_{i''t}^q, \dots$	1 if region n selected, 0 otherwise	$(1 - \alpha_c)(1 + r)^{T-t-k_{i''}+1} (nc_{i'',q}^{t+k_{i''}} x_{i'',t}^q) + \dots$	b_n

can be replaced by the following model without loss of generality:

$$Max Z = \sum_{c \in C} \sum_{p \in P} y_{pc} v_{pc} + \left(TB - \sum_{c \in C} \sum_{p \in P} y_{pc} w_{p,c} \right) (1 + r)^{T+1} \tag{18}$$

Subject to:

$$\sum_{c \in C} \sum_{p \in P} y_{pc} w_{p,c} \leq TB \tag{19}$$

$$\sum_{p \in P} y_{pc} = 1, \forall c \in C \tag{20}$$

$$y_{pc} \in \{0, 1\} \tag{21}$$

where P is defined as a set of calculated regions for the subsidiary c parametric problem and y_{pc} is a binary variable that refers to each computed region through the B&B algorithm; it is equal to 1 if region p is selected and 0 otherwise. Parameter v_{pc} is the value of the region p for the holding company and parameter w_{pc} is the lower bound of region p . Constraint (19) guarantees that the sum of the budget allocated to subsidiaries does not exceed the R&D budget and Constraint (20) guarantees that only one region must be selected from calculated regions for each subsidiary problem. Therefore, the proposed bi-level model is converted to 18–21 by considering computed solutions through the presented B&B algorithm for each follower’s parametric mixed integer model. Finally, Fig. 4 demonstrates the solution approach proposed in the present study.

5 Steps of the approach:

1. Set the allocated budget parameter B_{1c} space for each follower’s problem 5–16. [This step has already been done by adding constraint (17)]
2. Use the B&B algorithm and solve each follower’s parametric mixed integer model, individually.
3. Convert problem 1–17 into problem 18–21 by considering computed solutions for each follower.
4. Solve the mixed integer deterministic model 18–21.

6 Applying the model

This section demonstrates the power of programming through the implementation of the proposed model using a case study, which utilizes a pharmaceutical holding company as a case study. In addition to five subsidiaries that develop and manufacture new products, the holding company also distributes and markets its products. Manufacturing companies conduct research and development and develop new drugs. Further, the project’s pool of one distribution subsidiary is intended to facilitate the development of issues related to the pharmaceutical industry’s distribution system, including cold chain development. For the purpose of this study, we have used data from the holding company as a case study. During R&D projects, two types of resources are evaluated: the need for specialists and the need for laboratories.

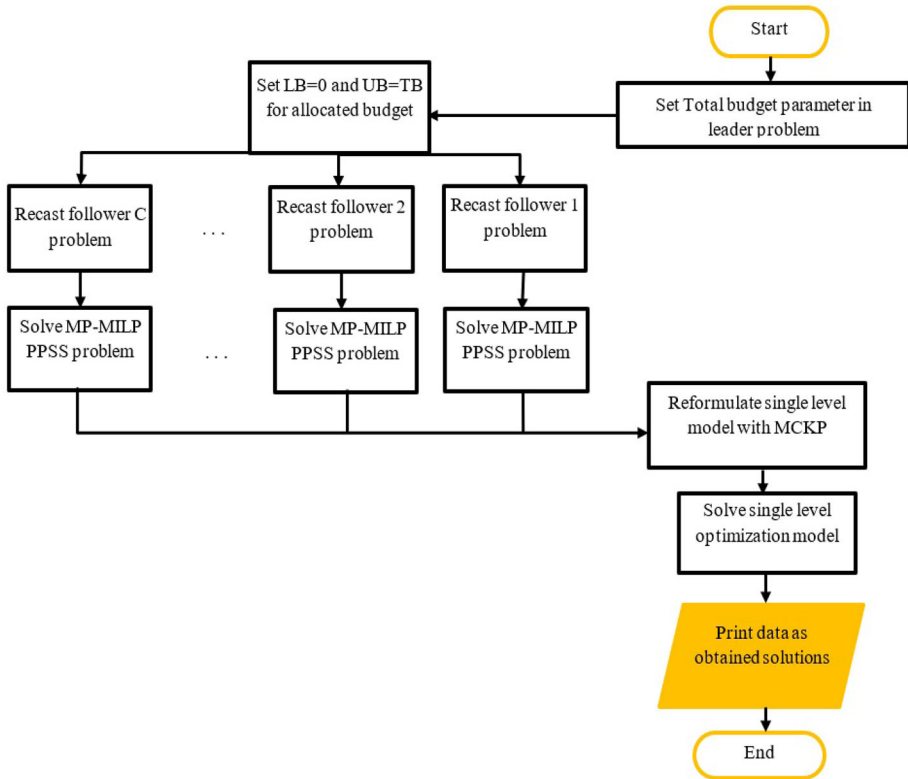


Fig. 4 Solution approach for bi-level multi follower PPSS problem

As mentioned earlier, the development of new drugs has four phases. As well as, there are potential projects with one or two phases to complete such as ongoing projects and the production of generic drugs. Pharmaceutical holding companies also have distribution and marketing subsidiaries. In such subsidiaries, there is also one stage to complete that pertains to the activities of the subsidiary. Moreover, the basket of projects in development subsidiary companies includes some projects with four development phases to complete. Table 6 presents information related to the subsidiaries of the holding company under study.

Data of the first subsidiary’s projects are presented in Table 7 (in the supplementary material, the data for all subsidiaries is presented). A subsidiary’s data set includes the cost to complete each phase and the number of resources needed to complete the phases. In addition, an early and late start year, resource requirements, loan limit in each period, and achievable income are defined for each project.

Economic parameters, including the interest and loan repayment rates, are explicitly defined for each industry. In the proposed decentralized structure, the total holding budget for R&D is apportioned among the subsidiaries. In the problem statement, \$120 million is earmarked to go to the subsidiaries (followers) to develop new products and development projects in the distribution company.

As explained in the previous section, each follower’s problem is reformulated with the allocated bounded budget. Then, the parametric B&B algorithm is used to calculate ranges for

Table 6 Information on the holding subsidiaries under study

Subsidiaries	Number of candidate projects	Holding share (percent)	Mission	Loan limit per period (\$ million)	Available specialists (number)	Available laboratories (number)
1	12	70	Product development	40	120	12
2	10	75	Product development	40	100	9
3	10	70	Product development	35	90	10
4	9	75	Product development	40	80	9
5	10	80	Distribution and Marketing	15	35	–

the budget. Therefore, the parameter on the right-hand side of Constraint (11) is reformulated with a lower bound of zero and an upper bound of \$120 million for each follower. Accordingly, the followers' models are transformed into a parametric model. Project selection and scheduling are based on different budget ranges for this model. In addition, each follower can finance itself up to the amount of its credit from external sources if this is profitable for the company.

Macroeconomic data should be established for the followers' problem. It is assumed that the amount of cash in the account to be carried over to the next period is increased by a rate of r (e.g., 4%) per period. In addition, the borrowed budget increases by a rate of δ (e.g., 10%) per period over the planning horizon. Development costs are also assumed to grow at a rate of λ (e.g., 2%) per year of delay beyond the current period. The values for development income are estimated by experts per project and decrease exponentially per period for a delayed start.

The holding company owns a percentage of the total share of the subsidiaries. Therefore, the revenues from completed projects are divided between a subsidiary and the holding company based on their respective shares. To illustrate, in the proposed model, the holding company owns 70%, 75%, 70%, 75%, and 80% of the total share of subsidiaries 1–5, respectively. Table 8 shows the results of the parametric linear PPSS model for subsidiary 1 and consequently the regions calculated for the bounded allocated budget parameter. It also shows the calculated regions and their associated allocated budget and value of each region for the holding company (by considering the holding company's share). Finally, the results of the parametric PPSS model (calculated regions) of each subsidiary are imported into model 18–22 as binary variables. By considering problem 18–21, only one region needs to be selected from each subsidiary's calculated regions. In light of the explanation in the previous section, the allocated budget for each subsidiary is the lower bound of the selected region. Thus, if the first region is selected by model 18–21, projects 3, 4, and 11 are scheduled with zero allocated budget (lower bound of the region); it means that subsidiary 1 can schedule projects 3, 4, and 11 without any budget allocated to it, thus it has to rely on loans.

Table 7 Data of subsidiary 1's projects

Project	Length of each stage (year)				Cost of each stage (\$ million)				Early start (year)	Tardy start (year)	Annual specialist requirement in stage/type				Annual laboratory requirement in stage/type				value of income
	I	II	III	IV	I	II	III	IV			I	II	III	IV	I	II	III	IV	
1.1	1	2	2	3	3	4	7	16	1	12	0	25	40	1	1.8	1.8	2	0	182
1.2	1	1	1	2	1	2	5	11	1	10	12	15	20	1	1.5	1.2	2.2	0	117
1.3	1	1	2	2	1	5	5	15	1	8	18	18	35	1	0.8	1.5	2.4	0	194
1.4	1	2	2	2	1	2	4	17	1	10	15	12	25	1	1	1.4	2	0	162
1.5	-	1	1	2	-	3	8	15	1	12	-	25	34	1	-	1.9	3	0	178
1.6	-	1	2	2	-	4	10	48	1	5	-	32	40	1	-	2	3.5	0	318
1.7	-	-	1	2	-	-	5	20	1	9	-	-	42	1	-	-	2	0	158
1.8	-	-	2	1	-	-	6	10	1	8	-	-	50	1	-	-	1.8	0	94
1.9	-	-	2	1	-	-	15	25	1	5	-	-	60	1	-	-	2.5	0	220
1.10	-	-	2	2	-	-	8	36	1	8	-	-	54	1	-	-	1.8	0	284
1.11	-	-	2	2	-	-	8	20	1	10	-	-	55	1	-	-	3	0	188
1.12	-	-	1	2	-	-	15	8	1	10	-	-	58	1	-	-	3.2	0	155

Table 8 Calculated solutions for P-MILP PPSS for subsidiary 1

Regions	Region of the allocated budget (parameter)	Scheduled projects in periods	Allocated budget if region selected	Value of this region for the holding company
1	$0 \leq B_{1,1} < 0.3$	3(5), 4(2), 11(1)	0	335.692
2	$0.3 \leq B_{1,1} < 0.32$	3(5), 4(1), 11(1)	0.3	401.367
3	$0.32 \leq B_{1,1} < 1.1$	2(3), 3(4), 4(2), 11(1)	0.32	345.324
4	$1.1 \leq B_{1,1} < 1.9$	3(4), 4(1), 11(1)	1.1	405.828
5	$1.9 \leq B_{1,1} < 3.53$	2(4), 3(4), 4(1), 11(1)	1.9	412.254
6	$3.53 \leq B_{1,1} < 3.97$	2(3), 3(4), 4(1), 11(1)	3.53	487.269
7	$3.97 \leq B_{1,1} < 4.96$	3(5), 4(2), 10(3), 11(1)	3.97	489.085
8	$4.96 \leq B_{1,1} < 5.74$	2(5), 3(1), 4(4), 5(5), 11(1)	4.96	553.705
9	$5.74 \leq B_{1,1} < 6.31$	3(4), 4(4), 5(4), 8(1), 11(1), 12(4)	5.74	615.761
41	$24.42 \leq B_{1,1} < 26.93$	3(3), 4(2), 5(3), 7(3), 10(4), 11(1), 12(1)	24.42	786.282
42	$26.93 \leq B_{1,1} < 28.45^*$	2(2), 3(3), 4(2), 5(3), 7(3), 10(5), 11(1), 12(1)	26.93	787.133
43	$28.45 \leq B_{1,1} < 29.73$	2(1), 3(3), 4(2), 5(3), 7(1), 10(4), 11(1)	28.45	800.120
60	$45 \leq B_{1,1} < 45.55$	2(4), 3(2), 4(2), 5(2), 7(5), 8(4), 10(3), 11(1), 12(1)	40	874.846
61	$45.55 \leq B_{1,1} \leq 120$	2(2), 3(2), 4(1), 5(2), 7(1), 8(4), 10(3), 11(1), 12(5)	45.55	877.523

Consequently, the selected region for subsidiary 1 is the region in row 42 of Table 8. In this region, the allocated budget is \$26.93 million and projects 2, 3, 4, 5, 7, 10, 11, and 12 are scheduled.

According to this explanation, the holding company under study has five subsidiaries named 1, 2, 3, 4, and 5. The basket of each subsidiary consists of 12, 10, 10, 9, and 10 projects that can be scheduled. Figure 5 shows the final solution of the bi-level multi-follower model. The final solution schedule for subsidiary 2 shows seven projects, 2.1, 2.3, 2.4, 2.6, 2.7, 2.8, and 2.10. Similarly, for subsidiaries 3, 4, and 5, seven, nine, and five projects, respectively, are scheduled in the planning horizon.

Figures 6 and 7 show the obtained cash flow of subsidiary 1 as the first follower of the proposed bi-level model. In the first period, the budget added by the leader is shown. Thus, in the optimal solution, \$23 million is used to schedule projects 11 and 12. Also, \$3.93 million is saved and carried over to the next period. In addition, in periods 2, 3, 4, and 5, the company must borrow from external funds to schedule new projects. The maximum loan amount for subsidiary 1 accrues in period 3, i.e., \$39.99 million. In addition, the revenues from completed projects are added to the cash flow of period six, and the additional cash of each period is carried over to the next period through inflation. It is quite clear: there is no need to borrow if the company has a positive amount in the account for one period. As a result, the objective function value of the first follower is \$255.916 million, which corresponds to an inflated amount of cash in the account in period 20. Similar to Fig. 6, the cash flows of followers 2–5 are shown in Fig. 8, 9, 10 and 11.

As explained earlier, each follower is influenced by the leader's decision, as well as vice versa, and seeks to maximize profits. Therefore, Table 9 compares the optimal amount of the budget allocated to each follower and the resulting optimal profits for the holding company

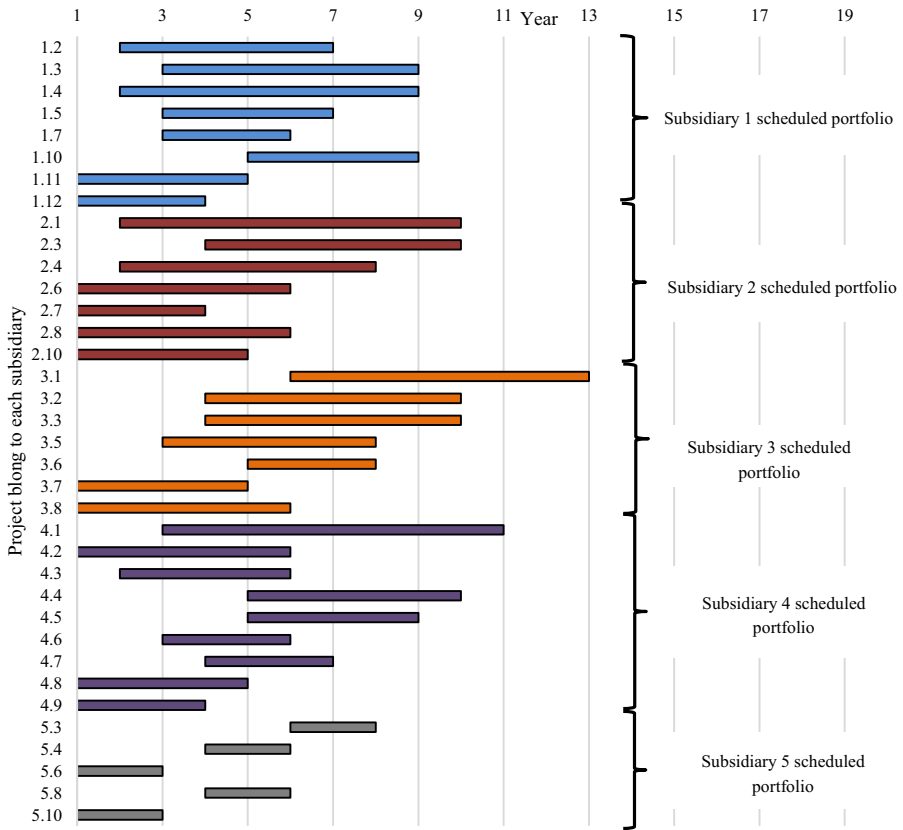


Fig. 5 Obtained solution for PPSS problem in the studied pharmaceutical holding company

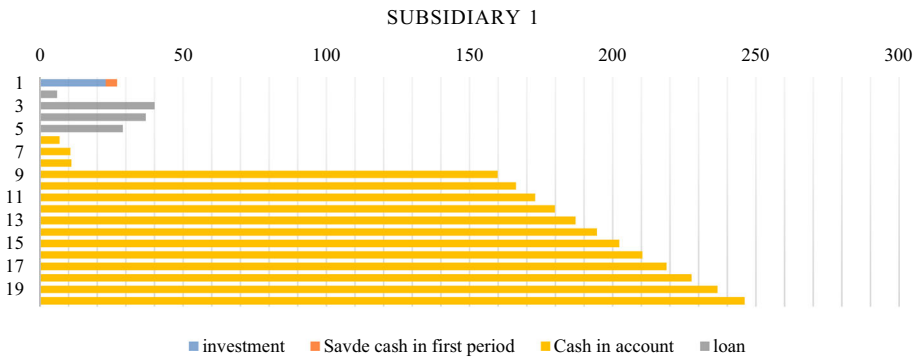


Fig. 6 Cash flow in each period for subsidiary 1

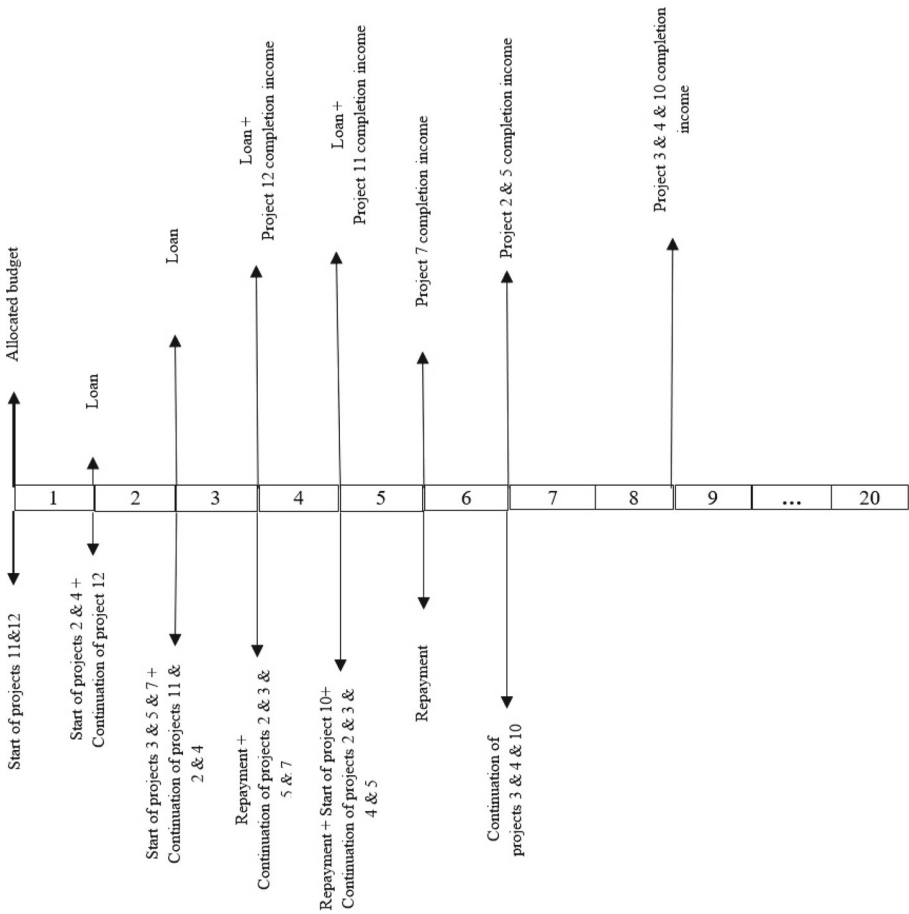


Fig. 7 Cash flow diagram for subsidiary 1

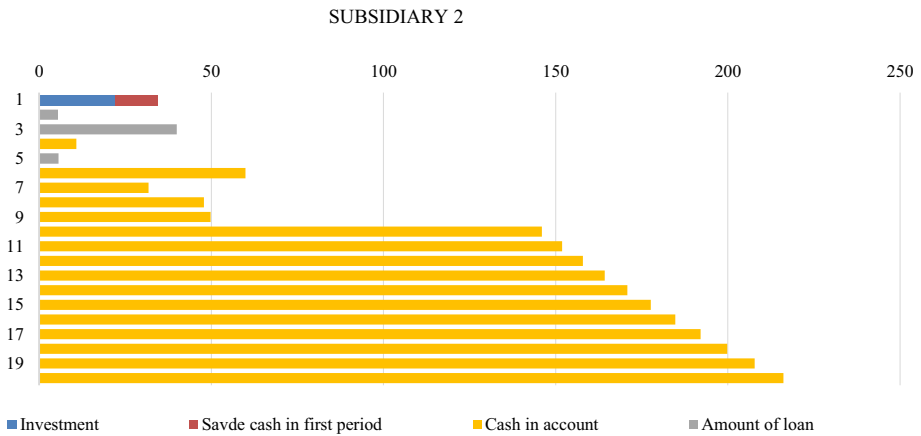


Fig. 8 Cash flow in each period for subsidiary 2

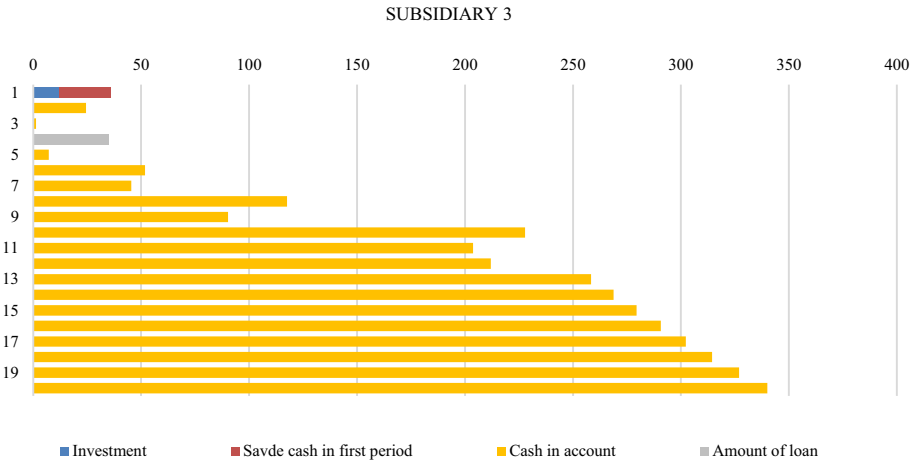


Fig. 9 Cash flow in each period for subsidiary 3

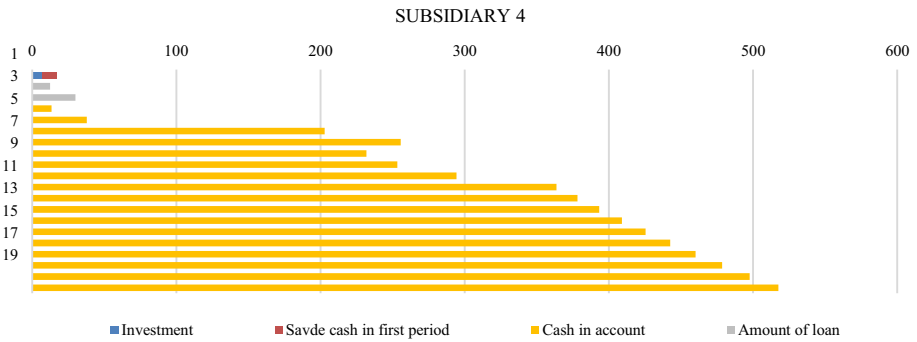


Fig. 10 Cash flow in each period for subsidiary 4

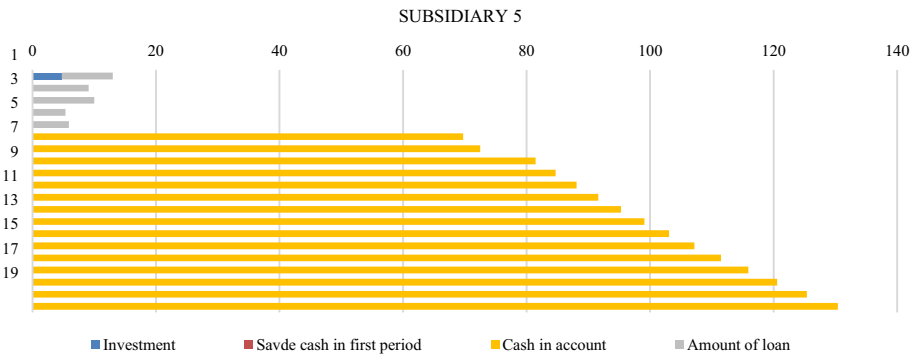


Fig. 11 Cash flow in each period for subsidiary 5

Table 9 Sensitivity analysis for different amounts of total budget

R&D budget (TB)	Leader's objective function		Follower 1		Follower 2		Follower 3		Follower 4		Follower 5	
	Objective function	Allocated budget	Objective function	Allocated budget	Objective function	Allocated budget	Objective function	Allocated budget	Objective function	Allocated budget	Objective function	Allocated budget
TB = 50	3731.87	125.175	6.31	127.314	10.94	229.550	18.22	469.057	9.73	135.609	4.74	
TB = 120	4559.83	255.916	26.93	224.764	34.22	353.667	35.56	538.303	17.11	135.609	4.74	
TB = 150	4614.37	301.016	37.79	233.960	36.04	370.690	39.37	538.303	17.11	134.552	15.87	
TB = 200	4737.36	301.016	37.79	233.960	36.04	370.690	39.37	612.800	42.19	134.552	15.87	

and subsidiaries for different amounts of the R&D budget. As shown in the table above, increasing the total budget increases the capital employed for each follower and leads to a better objective function for the players. However, increasing the total budget from 120 to 200 does not significantly impact the objective functions because the other resources are limited.

The financial and technical data of a pharmaceutical company with five subsidiaries were collected for implementation. The data included each subsidiary's project portfolio, projected cash flow, credit availability, and other resource requirements. The data were cleaned and prepared using Microsoft Excel 2016. The validity of the data was then verified with the management teams of each subsidiary. The final data was then fed into the proposed model. A hybrid approach was adopted to apply the model. The main algorithm was coded in Python and integrated with Gurobi solver to implement the solution approach shown in Fig. 5. A Windows 10-based LENOVO flex 5 with Intel Core i7 2.7 GHz and 16-GB RAM was used for the solution process, which was completed in 292 s. The optimal solution for the bi-level model was 4559.83, which is the maximum amount of cash in the account belonging to the holding company.

7 Conclusions and suggestions for further studies

This study first discussed the specific structure of holding companies. The subsidiaries of the holding company and the different structures between them and the upper-level decision makers were considered such that each subsidiary was affected by some strategic decisions of the upper level. However, the inner level companies had to make their own board decisions and tactical and operational decisions. The study also considered pharmaceutical holding companies, i.e., holding companies that develop new drugs, distribute pharmaceutical products, and perform other related functions. Pharmaceutical R&D is essential to healthcare delivery, and effective decisions can vastly improve a company's position both socially and financially. Not for nothing has the need for pharmaceutical R&D increased since 2019 with the outbreak of the COVID -19 pandemic and related diseases.

The structure of the proposed pharmaceutical holding company is to have two levels of decision makers. The first level is the leader (investment company), which decides on the strategic variables. Here, the leader decides how to allocate the R&D budget among the subsidiaries. The second level consists of several followers (subsidiaries) that decide on tactical and operational variables. Accordingly, the PPSS model was implemented for each follower, which is influenced by the leader's decisions.

The proposed decentralized optimization model employs a bi-level approach and a mixed-integer follower model in order to design the network. In the bi-level programming model, upper-level variables include the amount of cash in the holding company's account and budgeting, i.e., the amount of budget allocated to each follower, which is determined by the leader. Budgeting is the most strategic decision in the proposed structure for the problem under study. The rest of the decisions are up to the followers after the allocated budgets are determined. These decisions depend on the leader's decisions and are influenced by upper-level variables that are parameters in the inner level problem. Given the structure of the proposed bi-level model and the literature on such NP-hard problems, a hybrid approach was developed to find the solution. In this approach, the budget assigned by the leader was assumed to be the bounded parameter for the followers' problem, and the exact parametric mixed-integer linear programming algorithm was used within the range of the budget assigned by

the leader; therefore, the selected projects were also determined within the calculated range. Accordingly, multiple ranges were calculated for each follower. The leader's problem was then converted to a single level mixed integer model such that the lower bound of each range was the item's weight and the income of chosen projects was the item's value, since only one could be selected among multiple ranges for each follower. By reviewing the information of a pharmaceutical company that includes five subsidiaries, the values of the parameters for each project were determined.

The decentralized decision-making structure of holding companies has resulted in challenges between strategic and operational decision-makers. This study supports managers when making strategic and operational decisions in accordance with real-world features of holding companies. An analysis of this study sheds light on the alignment horizon between strategic decisions and operational decisions for managers of holding companies. While making strategic decisions in accordance with the holding's interests, subsidiaries' interests are also taken into account when making operational decisions.

Suggestions for further studies can be made from two different aspects. In the first section are the proposed aspects, assumptions, and solutions. The second aspect concerns the study of similar studies on the selection and scheduling of project portfolios with other structures, i.e., a meta-analysis. These two aspects are described respectively. The first proposal refers to mathematical techniques to add uncertainty to the proposed model. Robust methods can be used in fuzzy programming. However, new solutions to cope with the complexity of bi-level programming are essential. The first suggestion deals with the structured problem, which can be viewed as a group effort. Collaboration in the structured problem is another possibility. Logically, the subsidiaries in a group can collaborate in different ways. The literature on planning bi-level models for such situations discusses various types of collaboration, including semi-cooperative and reference cooperative models.

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