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Optimization-based Techniques for Production Scheduling of Continuous and Batch Processes

By

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Declaration of Authorship

I, Apostolos Elekidis, declare that this thesis titled, "Optimization-based techniques for production scheduling of mixed continuous and batch processes" and the work presented in it are my own. I confirm that:

- This work was done wholly while in candidature for a research degree at this University.
- Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated.
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"Since I grew tired of the chase and search, I learned to find;
and since the wind blows in my face, I sail with every wind.
You must be ready to burn yourself in your own flame.
How could you rise anew if you have not first become ashes?"

- Friedrich Wilhelm Nietzsche

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Στους γονείς μου Πάρη και Εύη,
για την απεριόριστη αγάπη τους
και όλη τους την υποστήριξη.
Στη Ματίνα,
για τη διαρκή στήριξη
και ενθάρρυνση

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ARISTOTLE UNIVERSITY OF THESSALONIKI

Abstract

Faculty of Engineering
Department of Chemical Engineering

Doctor of Philosophy

Optimization-based Techniques for Production Scheduling of Continuous and Batch Processes

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During the last few years, the significant advances of cutting-edge technologies led to a fourth industrial revolution, referred to as Industry 4.0. At the dawn of the new era of industrialization, modern production environments attempt to integrate various decisional and physical aspects of production processes into automated and decentralized systems. Two of the main decision levels in these systems, are production planning and scheduling, which constitute a major component for the efficient operation of the process industries. Especially in the current competitive globalized market, production planning and scheduling are of vital importance to most industries, since profit margins are miniscule. Therefore, efficient usage of resources has a critical role in the viability and sustainability of all industries. Additionally, efficiency targets are increasingly being adapted with sustainable production goals towards a green and circular economy. In addition to cost savings, further objectives must be considered, such as the reduction of greenhouse gas emissions, the increased usage of renewable energy sources and the reduction of waste.

These objectives can be achieved by exploiting recent advances of computer-aided optimization tools and methodologies. During the last 30 years plethora of research contributions have been published by the scientific community in the field of production scheduling optimization. However, the practical implementation of optimization-based

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scheduling frameworks in real-life industrial applications is limited. In most industries, the optimization of production scheduling constitutes an extremely challenging and time-consuming task, since the majority of decision-makers prefer to generate scheduling solutions manually, or use simulation-based software, resulting to suboptimal solutions.

This thesis proposes systematic mathematical frameworks for the optimization of a wide variety of complex production planning and scheduling problems. The optimization-based solutions are based on mixed integer linear programming (MILP) frameworks. However, a main drawback of MILP models is their inability to handle efficiently large problem instances, since the model size increases exponentially with the problem size. To face this challenge, novel MILP-based solution algorithms have been also investigated for the solution of real-life industrial problems.

More specifically, the first chapter considers the scheduling problem of a real-life large-scale industrial facility of packaged consumer goods. The problem under consideration is mainly focused on the packing stage which constitutes the major production bottleneck. Two precedence-based MILP mathematical models are proposed to describe explicitly the continuous process of the plant. The models rely on allocation, timing and sequencing constraints. Additional constraints, referring to the production/formulation stage of the plant, are also imposed in order to ensure the generation of feasible production schedules. Furthermore, two MILP-based decomposition algorithms are proposed for the efficient solution of large-scale problem instances. The applicability of the proposed approaches is illustrated by solving several real-life industrial problem instances of a multinational consumer goods industry under consideration. The results lead to nearly optimal scheduling in reasonable solution times, comparing favorably with manually derived schedules by the production engineers.

The second chapter addresses the scheduling problem of continuous make-and-pack industries, including flexible intermediate storage vessels, aiming to provide better synchronisation of the production stages. A novel continuous-time, precedence-based, MILP model is developed for the problem under consideration. Extending previously proposed precedence-based MILP models, multiple campaigns of the same recipe can be stored simultaneously in a storage tank. Explicit resource constraints related to the generation and recycling of byproduct are introduced, to achieve a better utilization of

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the available resources. Several case studies, inspired by a large-scale consumer goods industry have been solved, to illustrate the applicability of the proposed frameworks. Although global optimal solutions cannot be guaranteed, good quality schedules are obtained, while the utilisation of intermediate buffers leads to a better synchronisation of the production stages and increased productivity.

The final chapter of the thesis presents an integrated planning and scheduling framework for the optimal contract selection problem of Contract Manufacturing Organizations (CMOs) under uncertainty in pharmaceutical industry. During the last 20 years a growing number of pharmaceutical companies outsource part of their operations to reduce operational cost and mitigate their risk exposure. Contract Manufacturing Organizations (CMOs) utilize their facilities to manufacture products for multinational pharmaceutical companies on a contract basis. Considering a multistage, multiproduct, batch facility of a secondary pharmaceutical industry, an aggregated MILP planning model, including material balances and allocation constraints is firstly proposed. Using a rolling horizon approach, the production targets are then provided to a precedence-based MILP scheduling model to define batch-sizing and sequencing decisions in detail. To model demand uncertainty, a scenario-based approach is proposed, considering the Value-at-Risk (VaR) and Conditional Value-at-Risk (CVaR) measures. Since large number of scenarios introduces significant challenges to computations, a scenario reduction framework is integrated to reduce the total solution time, when considering large-scale problem instances. The proposed methodology increases the profitability of CMOs, by selecting the optimal contract combinations, depending on their risk tolerance, while considering the availability and optimal utilization of underlying production resources.

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Περίληψη

Το σύγχρονο βιομηχανικό περιβάλλον χαρακτηρίζεται από υψηλή αστάθεια, λόγω των ολοένα και ταχύτερα μεταβαλλόμενων οικονομικών και πολιτικών συνθηκών σε παγκόσμια κλίμακα. Έτσι, παρατηρείται μία ισχυρή κλιμάκωση του ανταγωνισμού μεταξύ των επιχειρήσεων, οι οποίες επικεντρώνονται ολοένα και περισσότερο στη διαρκή βελτίωση των διαδικασιών λήψης αποφάσεων.

Η ολοένα αυξανόμενη ζήτηση, σε συνδυασμό με τον υψηλό αριθμό τελικών προϊόντων, καθιστούν την κάλυψη πολλαπλών παραγγελιών μία σημαντική πρόκληση. Συνεπώς, για την επιτυχή ικανοποίηση των αναγκών των πελατών, είναι ιδιαίτερα σημαντική η αποτελεσματική χρήση του εξοπλισμού και η αποδοτική αξιοποίηση όλων των διαθέσιμων πόρων της παραγωγικής μονάδας, με απώτερο στόχο τη μείωση του κόστους παραγωγής. Την ίδια στιγμή, οι βιομηχανίες οφείλουν να συμμορφώνονται με τις ολοένα και πιο αυστηρές περιβαλλοντικές νομοθετικές ρυθμίσεις και να εντείνουν τις προσπάθειές τους για μείωση του ενεργειακού αποτυπώματος και των εκπομπών ρύπων. Με βάση τα παραπάνω, παρατηρείται μία σταδιακά εντεινόμενη προσπάθεια αυτοματοποίησης των διαδικασιών λήψης αποφάσεων, σε όλα τα ιεραρχικά επίπεδα, βασιζόμενη στην προοδευτικά αυξανόμενη χρήση νέων υπολογιστικών εργαλείων και τεχνολογιών αιχμής.

Ο χρονοπρογραμματισμός της παραγωγής αποτελεί ένα ζωτικής σημασίας επίπεδο λήψης αποφάσεων και διαδραματίζει σημαίνοντα ρόλο στην απόδοση μίας βιομηχανικής μονάδας. Αφορά την κατανομή των πόρων μεταξύ ανταγωνιστικών δραστηριοτήτων σε συγκεκριμένες χρονικές περιόδους, έχοντας ως στόχο τη βελτιστοποίηση ενός ή περισσότερων αντικειμενικών στόχων. Για τη βελτιστοποίηση του χρονοπρογραμματισμού παραγωγής καθίσταται απαραίτητη η μελέτη του συνόλου των διεργασιών που λαμβάνουν χώρα και οι αλληλεπιδράσεις τους με το ευρύτερο βιομηχανικό περιβάλλον.

Τα τελευταία 30 χρόνια έχει προταθεί ένα ευρύ φάσμα μεθόδων για την αντιμετώπιση αυτών των συνδυαστικών προβλημάτων, ωστόσο η πλειονότητα τους επικεντρώνεται κυρίως σε προβλήματα που δεν αποτυπώνουν την βιομηχανική πραγματικότητα. Τα προβλήματα χρονοπρογραμματισμού των σύγχρονων βιομηχανιών περιλαμβάνουν πληθώρα τελικών προϊόντων και μηχανολογικού εξοπλισμού, ενώ η παραγωγική

διαδικασία καθίσταται ιδιαίτερα περίπλοκη. Συνήθως τα προβλήματα αυτά υπόκεινται σε πολλαπλούς τεχνικούς και λειτουργικούς περιορισμούς, με αποτέλεσμα να χαρακτηρίζονται από εξαιρετικά υψηλή υπολογιστική πολυπλοκότητα και ως εκ τούτου δεν μπορούν να επιλυθούν σε χρόνους αποδεκτούς από την βιομηχανία. Σήμερα, στις περισσότερες βιομηχανικές μονάδες, το πρόγραμμα παραγωγής λαμβάνονται χειροκίνητα με τη μέθοδο της δοκιμής και σφάλματος, από εξειδικευμένους μηχανικούς παραγωγής, βασιζόμενοι κυρίως στην εμπειρία τους και τη χρήση περιορισμένου αριθμού βοηθητικών εργαλείων, όπως λογισμικά προσομοίωσης. Ως εκ τούτου, κρίνεται αναγκαία η ανάπτυξη νέων υπολογιστικών τεχνικών, οι οποίες θα οδηγούν σε υψηλής ποιότητας λύσεις σε σύντομο χρόνο, και κατά συνέπεια θα αποτελέσουν τη βάση για την ανάπτυξη αποτελεσματικών υπολογιστικών εργαλείων που θα συμβάλλουν σημαντικά στη βέλτιστη λήψη αποφάσεων. Με βάση τα παραπάνω, η παρούσα διατριβή επικεντρώνεται στην ανάπτυξη νέων μαθηματικών μοντέλων και τεχνικών, τα οποία λαμβάνουν υπόψιν όλα τα απαραίτητα χαρακτηριστικά ρεαλιστικών βιομηχανικών μονάδων, όσο και στην ανάπτυξη νέων αλγορίθμων για την επίλυση πολύπλοκων προβλημάτων μεγάλης κλίμακας, σε αποδεκτό από τη βιομηχανία υπολογιστικό χρόνο.

Ο προγραμματισμός παραγωγής αποτελεί ένα μόνο τμήμα της ιεραρχικής διαδικασίας λήψης αποφάσεων και περιλαμβάνει ένα μέρος των αποφάσεων που λαμβάνονται σε μία βιομηχανική μονάδα. Ένα ιδιαιτέρως σημαντικό επίπεδο αποφάσεων αποτελεί επίσης ο μακροχρόνιος σχεδιασμός παραγωγής (Planning). Σε αντίθεση με το χρονοπρογραμματισμό παραγωγής, όπου μελετάται συνήθως ένας χρονικός ορίζοντας έως και 2-3 εβδομάδων, ο σχεδιασμός της παραγωγής πραγματεύεται τη μελέτη ενός μακροχρόνιου χρονικού ορίζοντα, ο οποίος είναι σύνηθες να κυμαίνεται από μερικές εβδομάδες έως και 5 ή 10 έτη. Σε αυτό το επίπεδο, λαμβάνονται κυρίως στρατηγικές και οικονομικές αποφάσεις της εταιρείας, σχετικά με το σχεδιασμό και τη δυναμικότητα της βιομηχανικής μονάδας, τον προγραμματισμό για την αγορά προμηθειών και την παράδοση των παραγγελιών κτλ. Συνήθως, οι αποφάσεις του σχεδιασμού παραγωγής αποτελούν δεδομένα εισόδου για το ιεραρχικό επίπεδο του χρονοπρογραμματισμού. Η ταυτόχρονη μελέτη των δύο επιπέδων αποφάσεων (σχεδιασμός και χρονοπρογραμματισμός παραγωγής), παρουσιάζει σημαντικά πλεονεκτήματα έναντι της επιμέρους μελέτης των δύο προβλημάτων και μπορεί να οδηγήσει σε λύσεις οι οποίες στην πράξη αποδεικνύονται πιο αποτελεσματικές και περισσότερο εφαρμόσιμες. Μάλιστα, σε αρκετές βιομηχανικές μονάδες η επιμέρους μελέτη και επίλυση των δύο προβλημάτων μπορεί να οδηγήσει σε λύσεις οι οποίες είναι μη εφικτές στα κατώτερα επίπεδα λήψης αποφάσεων, όπως το επίπεδο του χρονοπρογραμματισμού παραγωγής. Στον αντίποδα, ένα σημαντικό μειονέκτημα που παρουσιάζουν οι ενοποιημένες προσεγγίσεις για την παράλληλη μελέτη των δύο προβλημάτων, είναι η ανάγκη για χρήση αυξημένου αριθμού μεταβλητών και περιορισμών, κάτι που επιφέρει υψηλότερη πολυπλοκότητα και καθιστά το ενοποιημένο πρόβλημα δύσκολα επιλύσιμο.

Λόγω της μεγάλης διάρκειας που απαιτείται για την ανάπτυξη νέων φαρμάκων και του υψηλού κόστους των κλινικών δοκιμών, το πρόβλημα του ενοποιημένου σχεδιασμού και χρονοπρογραμματισμού παραγωγής είναι ιδιαίτερα σημαντικό για τις φαρμακευτικές βιομηχανίες. Επιπλέον, κατά τη διάρκεια των τελευταίων 20 ετών, λόγω του έντονου ανταγωνισμού, παρατηρείται στη φαρμακευτική βιομηχανία μια αυξανόμενη τάση για υπογραφή συμβάσεων μεταξύ μεγάλων πολυεθνικών εταιρειών και εξωτερικών συνεργατών για την ανάθεση της παραγωγής των προϊόντων τους (Contract Manufacturing). Αυτό επιτρέπει στις φαρμακευτικές βιομηχανίες να επικεντρωθούν σε μεγαλύτερο χαρτοφυλάκιο προϊόντων χωρίς να αυξάνουν τις δαπάνες που συνδέονται με την κατασκευή νέων εγκαταστάσεων. Ωστόσο, η ζήτηση των φαρμακευτικών προϊόντων είναι ιδιαίτερα μεταβλητή, καθώς μπορεί να επηρεασθεί σημαντικά από απροσδόκητες παρενέργειες ή από τη χαμηλή δραστικότητα των νέων φαρμάκων. Ως εκ τούτου, οι εξωτερικοί συνεργάτες (Contract Manufacturing Organizations) οφείλουν να επιλέγουν το βέλτιστο συνδυασμό συμβολαίων/προϊόντων, ώστε να μεγιστοποιήσουν τα κέρδη τους λαμβάνοντας όμως υπόψιν και το υποκείμενο ρίσκο. Στη βιβλιογραφία, εκτενής αριθμός ερευνητικών εργασιών περιορίζεται κυρίως στη μελέτη των επιμέρους προβλημάτων του χρονοπρογραμματισμού ή του μακροχρόνιου σχεδιασμού παραγωγής της φαρμακευτικής βιομηχανίας. Ωστόσο, δεν εντοπίζεται κάποια εργασία η οποία να επικεντρώνεται στη μελέτη του ενιαίου προβλήματος του σχεδιασμού και χρονοπρογραμματισμού παραγωγής υπό αβεβαιότητα σε φαρμακευτικές βιομηχανίες και ειδικότερα, σε βιομηχανικές μονάδες που λειτουργούν κατ' ανάθεση παραγωγής φαρμακευτικών προϊόντων άλλων εταιρειών (Contract Manufacturing Organizations). Τα παραπάνω δημιουργούν ένα ερευνητικό κενό μεγάλου ενδιαφέροντος, ιδιαιτέρως λόγω των τελευταίων εξελίξεων και της κρίσης της φαρμακευτικής εφοδιαστικής αλυσίδας. Έτσι, στο τελευταίο τμήμα της διδακτορικής διατριβής μελετάται το ενιαίο πρόβλημα του σχεδιασμού και του χρονοπρογραμματισμού παραγωγής, σε βιομηχανικές μονάδες φαρμάκων υπό αβεβαιότητα της ζήτησης. Μελετάται επίσης το πρόβλημα της βέλτιστης επιλογής συμβολαίων για την παραγωγή προϊόντων σε βιομηχανικές μονάδες φαρμάκων, οι οποίες λειτουργούν κατ' ανάθεση παραγωγής φαρμακευτικών προϊόντων άλλων εταιρειών (Contract Manufacturing Organizations).

Όλα τα προτεινόμενα μοντέλα και οι αλγόριθμοι επίλυσης υλοποιήθηκαν με χρήση του λογισμικού GAMS και του επιλυτή CPLEX. Αναλυτικότερα, η συνεισφορά της παρούσας διδακτορικής διατριβής συνοψίζεται παρακάτω.

Αρχικά, μελετάται το πρόβλημα του βέλτιστου χρονοπρογραμματισμού παραγωγής σε βιομηχανίες πολλαπλών σταδίων παραγωγής, που περιλαμβάνουν διεργασίες συνεχούς λειτουργίας. Ειδικότερα, αναπτύχθηκαν δύο μαθηματικά μοντέλα Μεικτού-Ακεραίου Γραμμικού Προγραμματισμού (MILP) για την ελαχιστοποίηση του συνολικού χρόνου εναλλαγών (changeover minimization). Τα προτεινόμενα μαθηματικά μοντέλα αλληλουχίας (precedence-based), επικεντρώνονται στο στάδιο της συσκευασίας βιομηχανικών μονάδων καταναλωτικών αγαθών και βασίζονται σε μια σειρά από λογικούς αλλά και τεχνικούς περιορισμούς. Επιπλέον περιορισμοί, που αφορούν το συνεχές στάδιο παραγωγής των ενδιάμεσων προϊόντων, καθώς και περιορισμοί για τους χρόνους παράδοσης των προϊόντων, συμπεριλαμβάνονται προκειμένου να διασφαλισθεί η κατασκευή ρεαλιστικών προγραμμάτων παραγωγής. Για την επίλυση προβλημάτων προγραμματισμού παραγωγής μεγάλης κλίμακας σε βιομηχανικές μονάδες συνεχούς λειτουργίας, αναπτύχθηκαν επίσης δύο αλγόριθμοι βελτιστοποίησης. Ο στόχος των αλγορίθμων επίλυσης είναι η διάσπαση του αρχικού προβλήματος σε μικρότερα και ευκολότερα επιλύσιμα υποπροβλήματα (decomposition-based algorithm). Για την αξιολόγηση των προτεινόμενων μαθηματικών μοντέλων, και των αλγορίθμων επίλυσης, εξετάστηκαν διάφορα σενάρια ζήτησης και κατασκευάστηκαν προγράμματα παραγωγής για πάνω από 130 τελικά προϊόντα που παράγονται εβδομαδιαίως. Οι μελέτες υλοποιήθηκαν με τη χρήση ρεαλιστικών δεδομένων μιας βιομηχανικής μονάδας καταναλωτικών προϊόντων της εταιρείας Procter and Gamble (P&G). Τα αποτελέσματα αποδεικνύουν πως οι προτεινόμενοι αλγόριθμοι βελτιστοποίησης και τα μαθηματικά μοντέλα οδηγούν σε σημαντική μείωση του χρόνου εναλλαγών και συνεπώς σε αύξηση της παραγωγικότητας της μονάδας.

Επιπλέον μελετήθηκε ο βέλτιστος χρονοπρογραμματισμός παραγωγής σε βιομηχανίες συνεχούς λειτουργίας με δυνατότητα ενδιάμεσης αποθήκευσης και ανακύκλωσης παραπροϊόντων. Προτείνεται ένα νέο μαθηματικό μοντέλο Μεικτού-Ακεραίου Γραμμικού Προγραμματισμού (MILP), το οποίο αποτελείται από μια σειρά λογικών και τεχνικών περιορισμών, που σχετίζονται με την αλληλουχία των προϊόντων, τη διαθεσιμότητα των συσκευών, τους χρόνους παράδοσης των προϊόντων κ.α. Επιπλέον, το μαθηματικό μοντέλο βασίζεται σε συνεχή αναπαράσταση του χρονικού ορίζοντα, ενώ οι περιορισμοί των ισοζυγίων μάζας ικανοποιούνται μέσω της χρήσης ενός νέου συνόλου δυαδικών μεταβλητών. Τέλος, περιλαμβάνονται περιορισμοί για ρεύματα ανακύκλωσης των παραπροϊόντων, τα οποία παράγονται κατά τη διάρκεια των διεργασιών καθαρισμού των συσκευών. Παράλληλα, αναπτύχθηκε ένας αλγόριθμος βελτιστοποίησης (decomposition-based algorithm), για την επίλυση προβλημάτων χρονοπρογραμματισμού παραγωγής, βιομηχανικών μονάδων μεγάλης κλίμακας. Μελετήθηκαν προβλήματα μεγάλης κλίμακας, χρησιμοποιώντας ρεαλιστικά δεδομένα, από μία βιομηχανική μονάδα καταναλωτικών προϊόντων. Από την αξιολόγηση των εξαγόμενων λύσεων, συμπεραίνεται πως το προτεινόμενο μαθηματικό μοντέλο σε συνδυασμό με τις στρατηγικές επίλυσης, οδηγούν σε λύσεις που βελτιώνουν το συγχρονισμό μεταξύ των σταδίων παραγωγής, ενώ παράλληλα αυξάνουν την αποδοτικότητα του εξοπλισμού και τη χρήση των πρώτων υλών, μειώνουν το συνολικό κόστος και ελαχιστοποιούν τη παραγωγή παραπροϊόντων.

Στο τελευταίο τμήμα της διδακτορικής διατριβής μελετάται η βελτιστοποίηση του ενιαίου προβλήματος του σχεδιασμού και χρονοπρογραμματισμού παραγωγής σε βιομηχανικές μονάδες φαρμάκων υπό αβεβαιότητα. Αρχικά προτείνεται ένα μοντέλο Μεικτού-Ακέραιου Γραμμικού Προγραμματισμού (MILP), για το επιμέρους πρόβλημα του βραχυχρόνιου χρονοπρογραμματισμού παραγωγής σε μονάδες διαλείπουσας λειτουργίας. Το μαθηματικό μοντέλο, το οποίο βασίζεται σε συνεχή αναπαράσταση του χρονικού ορίζοντα, αποτελείται από μια σειρά περιορισμών, οι οποίοι σχετίζονται με την αλληλουχία των προϊόντων, τη δυναμικότητα των συσκευών, κ.α. Επιπροσθέτως, αναπτύχθηκε ένα μοντέλο Μεικτού-Ακέραιου Γραμμικού Προγραμματισμού (MILP), για το πρόβλημα του μακροχρόνιου σχεδιασμού παραγωγής σε βιομηχανικές μονάδες διαλείπουσας λειτουργίας. Το μαθηματικό μοντέλο, απαρτίζεται από μια σειρά περιορισμών, οι οποίοι σχετίζονται με τη διαθεσιμότητα και τη δυναμικότητα των συσκευών, τα ισοζύγια μάζας των υλικών, την αποθηκευτική δυναμικότητα της βιομηχανικής μονάδας κ.α. Για την επίλυση προβλημάτων μεγάλης κλίμακας, προτάθηκε ένας επαναληπτικός αλγόριθμος, ο οποίος βασίζεται στην τεχνική του κυλιόμενου ορίζοντα (rolling horizon). Παράλληλα, για τη μελέτη της αβεβαιότητας έγινε χρήση των εργαλείων μέτρησης κινδύνου, Value-at-risk (VaR) και Conditional Value-at-Risk (CVaR). Οι προτεινόμενες μαθηματικές τεχνικές εφαρμόστηκαν σε προβλήματα σχεδιασμού και χρονοπρογραμματισμού παραγωγής υπό αβεβαιότητα της ζήτησης, σε βιομηχανικές μονάδες παραγωγής φαρμάκων. Ειδικότερα, μελετήθηκε το πρόβλημα της βέλτιστης επιλογής συμβολαίων για την παραγωγή προϊόντων σε βιομηχανικές μονάδες φαρμάκων, οι οποίες λειτουργούν παράγοντας προϊόντα άλλων εταιρειών με εξωτερική ανάθεση (Contract Manufacturing Organizations). Μελετήθηκαν προβλήματα μεγάλης κλίμακας τα οποία περιλαμβάνουν πολλαπλά στάδια παραγωγής και μεγάλο αριθμό προϊόντων. Από την αξιολόγηση των εξαγόμενων λύσεων, συμπεραίνεται πως τα προτεινόμενα μαθηματικά μοντέλα, σε συνδυασμό με τις στρατηγικές επίλυσης, οδηγούν σε βέλτιστες λύσεις, λαμβάνοντας αποτελεσματικά υπόψιν το υποκείμενο ρίσκο.

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Apostolos P. Elekidis

June 2022

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Abbreviations

CMO	Contract manufacturing organization
COC	Changeover cost
CPU	Central processing unit
EMA	European medicines agency
ERP	Enterprise resource planning
FDA	Food and Drug Administration
FMCG	Fast moving consumer goods
IMP	Immediate precedence model
ITC	Idle time cost
MES	Manufacturing execution system
MILP	Mixed integer linear programming
PSE	Process systems engineering
PTC	Processing time cost
R.M.U.	Relative monetary units
RTN	Resource task network
STN	State- task network
TC	Total cost
TSP	Travelling salesman problem
USGP	Unit-specific general precedence model
WC	Waste cost

1

Introduction

1.1 Motivation and objectives

Nowadays, due to the ever-increasing competition, process industries face multiple tough challenges. Hence, decision-makers put massive effort to increase profit margins by allocating more efficiently the available resources between competing activities and reducing the various costs. However, in the new era of manufacturing processes, goals of efficiency are now being complemented by sustainable production objectives. Besides cost reduction, further benefits can be achieved by using cutting-edge technologies, such as time reduction, predictive maintenance, reduction of the environmental footprint, and better supply chain visibility. Following the recent advances of the Fourth Industrial Revolution (Industry 4.0), modern process industries are obliged to invest in research and development to digitalize the various decision-making processes (Rossit et al., 2019). Furthermore, due to the tremendous volatility of the global market, the coordination of different decision levels has a vital role in the sustainability of process industries (Harjunkoski et al., 2014). Production scheduling constitutes a crucial decision level, as it has a direct impact on the overall efficiency of all industrial facilities. Critical objectives can be achieved via optimal production schedules, according to the current needs of the plant, such as the reduction of production cost or production downtimes, and the minimization of energy consumption. Hence, during the last three decades a plethora of mathematical frameworks has been proposed to face the production scheduling optimisation problem. The vast majority of these approaches rely on mixed-integer linear programming (MILP) formulations, since it proved to be extremely flexible and accurate, while ensuring optimal solutions (Georgiadis et al., 2019a; Harjunkoski et al., 2014).

Within the overall current climate of business globalization, modern industrial facilities have to satisfy a highly diversified product portfolio that can address the needs of customers. Current real-world industrial applications include hundreds of different final products in flexible facilities, under several tight design and operational constraints. As a result, several companies from various industrial sectors, such as food and beverages, pharmaceuticals, chemicals and fast-moving consumer goods (FMCGs), have adopted continuous make-and-pack production layouts (Castro et al., 2018; Méndez et al., 2006).

The utilization of continuous processes can lead to notable benefits for process industries. Firstly, continuous processes can increase the production throughput, by reducing the total processing time. Aside from time saved, industries decrease the total energy consumption by avoiding shutting down and resetting machines repeatedly. Furthermore, once a continuous equipment starts to operate, only a general supervision of the machinery is required. This allows for labour costs reduction and therefore research and development expenditures can be increased (Harjunkoski et al., 2014).

Despite the multiple advantages, scheduling optimization of continuous processes is a tough task. Usually, the synchronization between stages cannot be easily achieved and due to different production rates undesirable idle times are realized. Hence, modern industrial facilities consist of complex production layouts that include several production routes, flexible storage vessels and recycling streams to increase the overall productivity. However, it can be noticed that scheduling optimization of continuous processes, has received only a small attention in comparison with batch facilities (Castro et al., 2018; Harjunkoski et al., 2014; Méndez et al., 2006). Therefore, the development of efficient mathematical frameworks for the optimal production scheduling of multistage continuous processes is a known research gap. Concerning the above observation, novel mathematical frameworks are proposed in this thesis, for the optimal scheduling of multistage continuous processes.

Although digitalization has attracted a lot of attention within various industrial sectors, in terms of production scheduling the reality is not so encouraging. In practice production schedules are mainly manually generated, based on the experience of production engineers. Therefore, production scheduling is a time-consuming process as a lot of manpower is wasted to obtain even a feasible or sub optimal solution. Additionally, due to unexpected events, such as order cancelations or equipment breakdowns, the initial solution must be updated in weekly or even in daily basis. Simulation tools (e.g., SchedulePro™) constitute a useful tool as fast and feasible

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solutions can be generated, although without ensuring optimality (Koulouris et al., 2021; Papavasileiou et al., 2007). Concerning the above facts, it is concluded that there is a strong need to develop efficient mathematical frameworks that lead to nearly optimal solutions in small computational times. Although numerous MILP models can be found in the open literature, only a few industrial applications have been reported. It can be noticed that most of the optimization methods have efficiently handled small or medium sized problem instances, while only a few of them have been applied in large scale industrial problems (Castro et al., 2018; Georgiadis et al., 2019a). Hence, due to the lack of real-life applications, this thesis proposes efficient MILP-based solution algorithms for the scheduling of real life, large-scale, industrial problems.

Finally, among different industrial sectors pharmaceutical industry is composed of many challenging planning and scheduling problems possessing both industrial and academic significance (Sarkis et al., 2021; Shah, 2004). Over the past few years, large R&D pharmaceutical companies have increasingly outsourced non-core activities, such as manufacturing, to Contract Manufacturing Organisations (CMOs). CMOs are companies without their own product portfolio and serve other companies in the pharmaceutical industry on a contract basis to provide comprehensive services related to drug manufacturing. This policy enables multinational pharmaceutical industries to reduce their costs and emphasise on drug discovery and marketing, which are considered as key parts for their value chain (Jarvis, 2007). A contract can include currently developed products, characterized by highly volatile demand and high selling prices, or drugs with less uncertain demand and lower profit margins. Typically, drug development is a time-consuming process, as it takes at least 10 years on average for a new medicine to be in the marketplace. Additionally, demand of newly developed pharmaceutical products is usually highly uncertain. Lower drug efficacy can affect the demand and total sales, while in the worst case, it can lead to the suspension or even the withdrawal of the drug. Under this dynamic and uncertain environment, a CMO must decide the best contract combination to accept, so as to maximize its profits. Although multiple research contributions are focused on the short-term scheduling of pharmaceutical industries (Kopanos et al., 2010a; Stefansson et al., 2006) or the planning of clinical trials (Colvin and Maravelias, 2011; Levis and Papageorgiou, 2004), only a handful of them considered the integrated planning and scheduling problem, while the optimal contract selection problem of CMOs under uncertainty in the

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secondary pharmaceutical industry has never been addressed. Hence, the scientific knowledge is expected to be broadened with the introduction of an optimization-based framework for the optimal contract appraisal of CMOs in the secondary pharmaceutical industry under demand uncertainty.

The main objectives of this thesis are:

- The development of novel MILP-based models for the optimal production scheduling of multistage continuous processes, while considering flexible intermediate storage vessels, aiming to provide better synchronization of the production stages.
- The efficient modelling of byproducts recycling streams to reduce waste, environmental footprint and production cost.
- To propose efficient MILP-based solution strategies for the solution of large-scale industrial problem instances.
- The development of integrated planning and scheduling optimization frameworks considering uncertainty for multistage batch plants of the secondary pharmaceutical industry.
- To propose an efficient MILP-based optimization approach for the optimal contract selection problem of Contract Manufacturing Organizations in the pharmaceutical industry under demand uncertainty.
- To reduce the existing gap between scientific research and industrial reality by successfully applying the proposed mathematical frameworks in real-life, large-scale industrial cases studies, either using real industrial data, or data that correspond to real-life conditions.

1.2 Production scheduling

Scheduling is concerned with the allocation of scarce resources among competing activities over time. It is a decision-making process aiming to optimize one or more objectives by taking into account the processes taking place and their interactions with the environment. Scheduling problems exist in many manufacturing and production systems, in transportation and distribution of people and goods, and in other types of industries. The three elements which need to be mapped out are time, tasks and resources: The time at which the tasks have to be performed needs to be optimized considering the availability and restrictions on the required resources. The resources may include processing, material storage and transportation equipment, manpower, utilities (e.g., steam, electricity), any supplementary equipment and so on. The tasks typically include processing operations (e.g., reaction, separation, blending, packaging) as well as other activities like transportation, cleaning in place, changeovers, etc., (Kallrath, 2002). Both external and internal elements of the production need to be considered. The external element originates from the need to co-ordinate manufacturing and inventory levels based on a given demand, as well as arrival time of raw materials and even maintenance activities. The internal element considers the execution of tasks in an appropriate sequence and time, while taking into account all external considerations and resource availabilities. Overall, the sequencing and timing of tasks over time and the assignment of appropriate resources to the tasks must be performed in an efficient manner, that will, as far as possible, optimize a given objective. Typical objectives include the minimization of cost or maximization of profit, the maximization of throughput, the minimization of tardy jobs, etc., (Méndez et al., 2006).

Flexible multipurpose plants are able to produce a wide range of different products using a variety of production routes. This characteristic makes such plants particularly effective for the manufacture of classes of products that exhibit a large degree of diversity, and which are subject to fast-varying demands. Due to their inherent flexibility, the scheduling of such plants is a problem of high complexity. Compared to other parts of the supply chain management (e.g., distribution management and inventory control), the production scheduling is often by far the most computationally demanding part. The most general "multipurpose" plants can be viewed as collections of production resources (e.g., raw materials, processing and storage equipment, utilities, manpower) shared by several processing operations, that manufacture a number of products over a given time horizon. The process may include several intermediates that lead to multiple final products, recycles of byproduct materials, and multiple routes to the same final product. Single or multiple stage multi-product plants are thus special cases of multipurpose plants. Concerning the above facts, even the most trivial scheduling problems are NP-hard, thus no known solution algorithms exist that are of polynomial complexity in the problem size. This has posed a great challenge to the research community, and multiple research contributions have arisen aiming to develop

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either tailored algorithms for specific problem instances or efficient general-purpose methods. Although the first approaches have been focused on providing generic mathematical models, during the next years this endeavour has been abandoned, since the research community focused on exploitation of problem-specific mathematical frameworks.

1.2.1 Classification of Scheduling Problems

Usually, scheduling problems are defined by three main elements. The production environment, the special characteristics of process industry (production constraints) and the main objective under consideration (e.g., minimization of cost). Since the entries of these elements are extremely diverse among process industries, many classes of scheduling optimization problems exist. In particular, scheduling problems can be defined by the following inputs:

- Data related to production facilities, such as processing stages, production equipment, storage vessels, processing rates and unit to task compatibility.
- Availability of resources such as raw materials, utilities, and manpower
- Production or inventory targets that need to be satisfied.

The first terms can be usually considered static since they remain fixed for all problem instances of a facility unless any redesign studies are considered. On the other hand, the other terms are usually defined by other decision-levels, such as production planning and control. Therefore, scheduling is not a standalone problem; it is part of the overall manufacturing supply chain, and it is strongly connected to other functions (see Figure 1.1).

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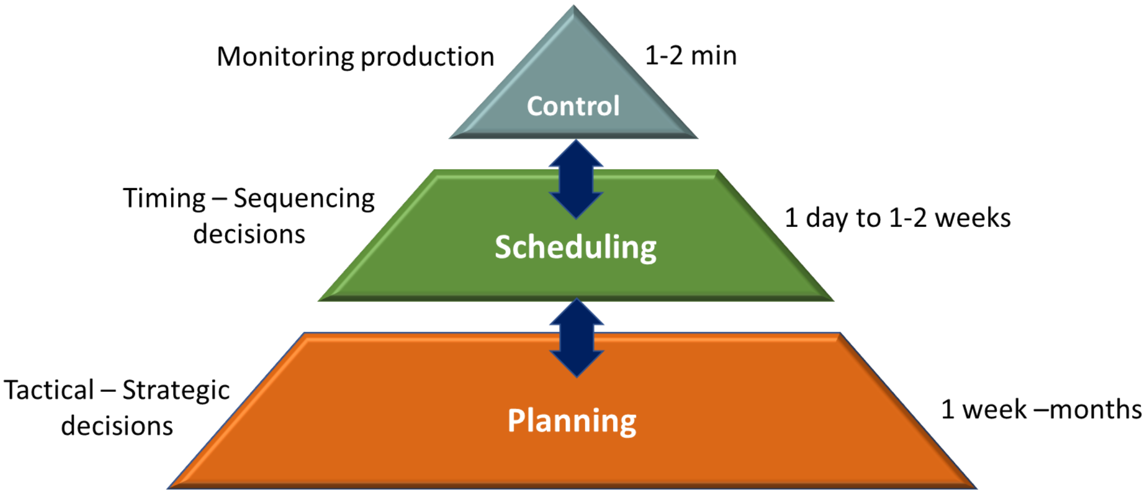

Figure 1.1 Information flow towards scheduling level

The scheduling decisions seeks to optimally answer to the following questions:

- What tasks must be executed to satisfy the given demand and the production targets (batching/lot-sizing)?
- Which resources must be used?
- How many and what kind of batches/lots must be produced?
- In what sequence are batches/lots processed?

The most common objective is the maximization of the total profit, while respecting all operational, logistical and technical constraints. However other objectives such as the minimization of the total cost, earliness and/or tardiness, and production makespan are also considered depending on the current needs of the industry. The main scheduling decisions are also illustrated in Figure 1.2.

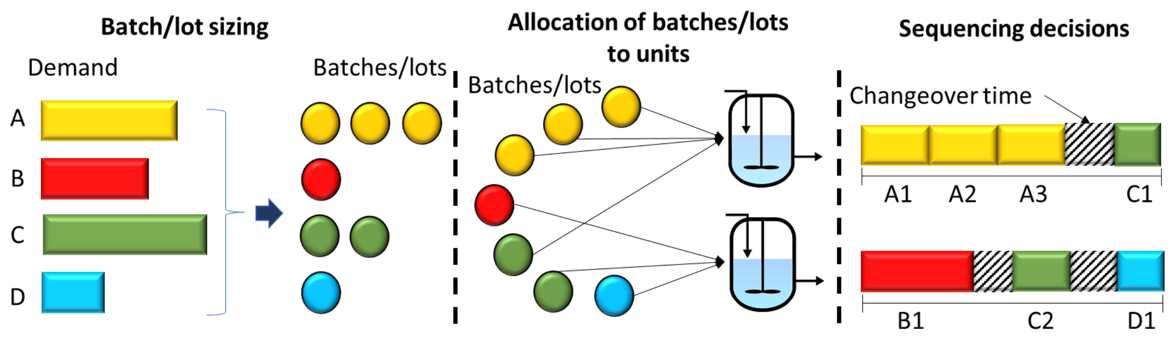

Figure 1.2 Main scheduling decisions

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It should be noted that depending on the specifics features of each problem, some of the aforementioned decisions are not considered in the scheduling level. The development of a scheduling model requires the consideration of all essential production features to ensure the feasibility of the proposed schedules. However, the production should be represented in the simplest way to reduce the computational complexity of the problem. This is vital when solving real-life industrial problems, which typically includes a huge number of products and constraints that must be satisfied. The scheduling problems found in process industries are classified in terms of: (a) the production facility and (b) the specific processing characteristics and constraints. As a result, several modelling frameworks have been proposed by the research community. A short description of these terms is presented in the following subsections, while an interested reader can find more details in the excellent reviews of Harjunkoski et al., (2014) and Georgiadis et al., (2019a).

1.2.2 The production facility

The production facilities can be classified based on the type of the processes and the production environment. It should be noted that many scheduling problems consider the optimization of material transfer operations rather than production operations. Indicative examples are the crude oil and pipeline scheduling. However, these problems are out of the scope of this thesis. Therefore, the following analysis is focused on production scheduling of process industries.

1.2.2.1 Process type

The main types of production process found in the process industries can be defined as continuous or batch. In continuous operations, raw materials are continuously provided into processing units resulting in a constant flow. Continuous processes are ideal for mass production of similar products because they can ensure product quality consistency while lowering manufacturing costs due to economies of scale. On the other hand, in batch processes all components must be completed at a unit before they continue to the next one. Batch processes are often chosen for production of high-added value products as they can ensure the required purity and the quality of products. Batch operations are also appropriate for the production of products that described by seasonal demand (e.g., large batches of one product are made for sale in the summertime). Batch and continuous processes both necessitate the same types of decisions in terms of scheduling. Batches in batch processing and lots in continuous processing are the two types of tasks. In continuous processes, assignment (of batches/lots to units), sequencing (between batches/lots), and timing (of batches/lots) decisions are identical, whereas task selection and sizing (batching/lot-sizing) have more degrees of freedom. In continuous processes, capacity restrictions refer to processing rates and times, which are usually unrestricted, so a given order can be fulfilled in a single lot (campaign) or multiple shorter ones. Batch production, on the other hand, is limited by the amount of processed material that a unit can handle, affecting the number and size of batches that must be scheduled. Another distinction lies in the way inventory levels are affected. It's worth noting that many facilities are characterized by multiple types of processes. For example, in "make-and-pack" production facilities, multiple batch or continuous processing phases are followed by a packaging (continuous) stage. This production layout is highly frequent in the food and beverage and consumer goods industries, and it necessitates the consideration of both batch and continuous manufacturing processes.

1.2.2.2 Production environment

Production facilities can be classified as sequential or network, based on material balance constraints. In sequential processes each batch/lot follows a set of production steps based on a specific recipe. In this industries batch mixing/splitting is not allowed. Network facilities are more general and complex, and their topology is usually arbitrary. Furthermore, there are no limitations on the handling of input and output materials, so mixing and splitting operations are allowed.

Sequential facilities can be divided into the following categories based on their topological characteristics:

- ***Single stage***: A production facility with only one processing stage, which can be a single unit or multiple parallel units. The product-to-unit compatibility can be fixed (each batch must be processed in a single unit) or flexible (each batch can

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be processed in multiple units), but each batch must be processed in a single unit in all cases.

- **Multistage**: Each batch must be processed in multiple stages, each of which may consist of a single unit or multiple parallel units.
- **Multipurpose**: When routings are product-specific, or when a processing unit belongs to different processing stages depending on the product, a facility is described as multipurpose, and it is equivalent to jobshop environments in discrete manufacturing.

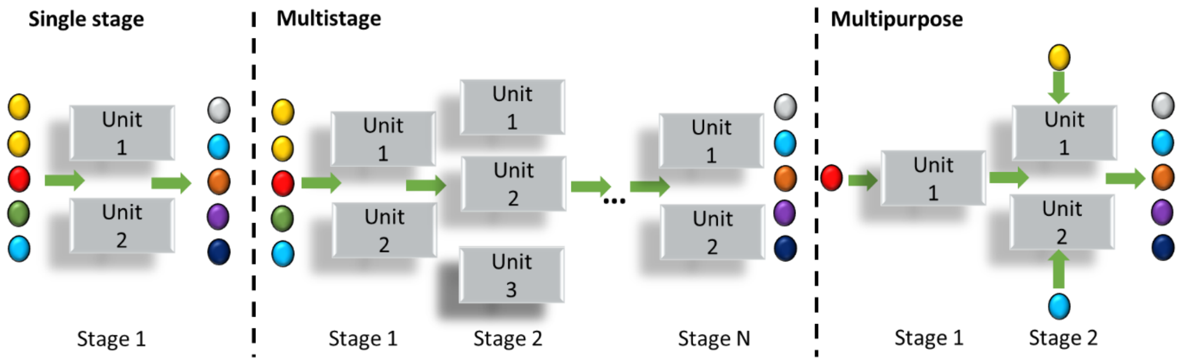

Figure 1.3 Categorization of scheduling problems based on their topological characteristics

The majority of early research focused on sequential facilities (Egli and Rippin, 1986; Vaselenak et al., 1987). Process industries that operate in a sequential environment are quite similar to discrete manufacturing, and there are many similarities to be found when describing them. Sequential facilities can be simply represented in terms of batches and production stages. However, this is not applicable for network facilities, so they cannot be modelled in the same way. The representations of the State task network (STN) (Kondili, E., Pantelides, C. and Sargent, 1993), and the Resource Task Network (RTN), (Pantelides, 1994), were the first to propose general representations of network facilities. Both contributions constitute the cornerstone of research advance since most existing approaches rely on these concepts. A classification of the scheduling problems based on their topological characteristics is illustrated in Figure 1.3.

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1.2.3 Processing characteristics and constraints

Scheduling problems may refer to facilities that described by various special processing features and constraints. These aspects increase the complexity of the problem but must be taken into account, in order to guarantee the feasibility of the generated production schedules. A brief presentation of these features is given in this section while a detailed description is provided by Méndez et al., (2006).

Resource considerations, aside from task-unit assignments and task-task sequences, are of great importance. These may involve auxiliary units (e.g., storage vessels), utilities (e.g. steam and water) and manpower. Resources are mainly classified into renewable (recover their capacity after being used in a task, e.g. labor) and non-renewable (their capacity is not recovered after being consumed by a task, e.g. raw materials). Renewable resources can be further classified into discrete (e.g. manpower) and continuous (e.g. electricity, cooling water). Another important characteristic in process industries is the handling of storage, which is usually referred to as the storage policy. Depending on the duration a material can be stored, the storage policies are described as i) Unlimited Intermediate Storage (UIS), ii) Non-Intermediate Storage (NIS), (iii) Finite Intermediate Storage (FIS) and (iv) Zero Wait (ZW). Setups are a critical factor in most processing facilities as they represent operations like re-tooling of equipment, cleaning or transitions between steady states. They are associated with a specific downtime that can be sequence-independent or sequence-dependent (changeovers) and a cost is induced to the production process. To reduce the complexity associated with the consideration of setups, products are categorized into families. In that case setups exist only between products of different families.

This categorization shows the complexity of scheduling problems and the huge diversity of characteristics that must be accounted for when facing real-life industrial problems. The inherent diversification of scheduling problems in the process industries hindered the initial efforts of the academic community to propose a generic mathematical framework. Therefore, research turned into the development of less general methods that can address industrial cases that share similar characteristics. As a result, a multitude of efficient specialized methods for the optimization of scheduling in the process industries have been proposed in the last 30 years.

1.2.4 Classification of modelling approaches

As it is described in the previous subsections, scheduling optimization is affected by extremely diverse features. The initial attempts of developing a generic mathematical model, that would be efficiently applied to all scheduling problems were proven unsuccessful and soon the research community focused on the exploitation of more problem-specific mathematical formulations and solution algorithms. The computational complexity of scheduling problems gave rise to numerous optimization approaches. Although this thesis is focused on the MILP-based approaches, it should be mentioned that a plethora of alternate approaches is also proposed in the open literature. In particular, constraint programming models (Malapert et al., 2012; Zeballos, 2010), heuristic (Aguirre et al., 2017; Bilgen et al., 2014) and metaheuristic approaches (Subbiah et al., 2009; Zobolas et al., 2009) have been developed. The main advantage of these methods is their ability to generate fast and feasible solutions. Hence, they constitute a very attractive option for industrial problem instances. However, their main drawback is related to their inability to ensure the optimality of the generated schedules. To combine the advantages of both MILP models and non-optimization approaches, hybrid methods have emerged that are able to provide near-optimal solutions in low computational time (Baumann and Trautmann, 2014; Georgiadis et al., 2021; Kopanos et al., 2010a).

The three main aspects that describe all optimization models for scheduling are: (i) the optimization decisions to be made, (ii) the modelling elements and (iii) the representation of time. A detailed presentation of the main modelling approaches is given by Méndez et al., (2006).

1.2.4.1 Optimization decisions

The optimization decisions may differ depending on the needs and the policy of each industry. One important aspect is the consideration of batch/lot sizing decisions. In particular, the number and the size of batches (or lots) can be either defined in the planning or scheduling level. In the first case the number and the size of batches/lots is prefixed and constitute one of the main inputs of the scheduling optimization model. On the other hand, the consideration of batch or lot sizing decisions in the scheduling model allows for further flexibility and can led to better solutions. The number and size

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of batches can be also defined heuristically by decision-makers. Then an optimization approach for the unit allocation, sequencing and timing decisions can be applied. This approach is common in models for sequential environments where batch mixing or splitting is not allowed. In contrast, a monolithic approach, consisting of batching/lot-sizing, unit assignment, sequencing, and timing decisions, is used for network environments (Georgiadis et al., 2019a).

1.2.4.2 Modelling elements

According to the entity used to handle the mass balance constraints, scheduling models are classified into batch-based and material-based. In sequential environments, where the identity of each batch remains the same throughout the processing stages, batch-based approaches are mainly chosen in sequential environments, where the identity of each batch remains the same throughout the processing stages. On the other hand, material-based approaches tend to be more suitable, when dealing with network environments, that includes several mixing operations, recycling streams and more complex production routes. It is important to mention that the modelling elements used are also strongly connected to the optimization decisions. In particular, in monolithic approaches the scheduling problems are modelled using a material-based approach, while a batch-based approach is followed, whenever the batching decisions are known a priori. However, batch-based approaches that consider batch sizing decisions have been also proposed (Cerdá et al., 2020; Kopanos et al., 2010b; Méndez and Cerdá, 2002a)

Batch-based approaches are mainly relied on the representation of processing stages, processing units in each stage and batches or products (depending on whether batching decisions are prefixed or not). The second type of representation emerged in the early 90s from the novel works of Kondili, E., Pantelides, C. and Sargent, (1993), and Pantelides, (1994),who introduced the STN and RTN, both based on the modelling of materials, tasks, units and states. The STN represents manufacturing processes as a collection of material state{s (feeds, intermediate final products) that are consumed or produced by tasks. The main difference between STN and RTN is that in the latter states, units and utilities are represented uniformly as resources that are produced and consumed by tasks. While both STN and RTN representations was initially introduced

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for scheduling problems in network environments, recent works have addressed problems in sequential environments (Lee and Maravelias, 2017).

1.2.4.3 Time representations

The most important element and the one that mostly differentiates optimization models for scheduling is the representation of time. Modelling frameworks can be mainly categorized into two main approaches. The precedence-based and the time-grid-based.

Precedence-based MILP models relies on binary sequencing variables that denotes the sequence of batches or products. Based on the type of the precedence variables, precedence-based models can be further divided into general, immediate and unit-specific general precedence models. The majority of these models consist of product (or batch) to unit allocation, timing and sequencing constraints (Méndez et al., 2006). In general precedence models, precedence relationships are established between all pairs of batches/lots while in immediate precedence models, the precedence relationship is established only between consecutive pairs. Typically, general precedence models include fewer binary variables, and therefore they are more computational efficient. One of the main drawbacks of general precedence models is their inability to identify subsequent tasks, and therefore to consider changeover costs and heuristics, such as pre-fixing or forbidding certain processing sequences (Cerdá et al., 2020). To overcome this limitation immediate precedence formulations can be utilized. Furthermore, in order to combine the advantages of both approaches, unit-specific general precedence approaches have been proposed that combines both general and immediate sequencing variables (Kopanos et al., 2010a). One of the main disadvantages of precedence-based models is the dramatic increase of the size of the model when considering large number of batches/products. The use of heuristics such as product families or pre-fixing of sequences mitigates this phenomenon and enormously improves the efficiency of these models (Kopanos et al., 2010b).

Time-grid-based models can be classified into discrete and continuous, while continuous-time formulation may employ single or multiple-time grids. Although numerous discrete and continuous-time models have been presented, the selection of time representation is still an open issue. Continuous-time formulations are not necessarily more efficient than discrete-time models, since the selection of the most appropriate time representation is strongly dependent on the scheduling problem under consideration (Castro et al., 2009c; Maravelias and Grossmann, 2003). A great variety of time-grid-based approaches exist depending on the representation of events, such as time slots, global periods and time points. In discrete-time models the time-grid is divided into a pre-defined number of time periods with a given and known duration, both of which need to be specified by the model developer. Most discrete formulations use a common time grid for all resources. However, Velez and Maravelias, (2013), proposed discrete-time models that utilize multiple time frames. One of the main challenges in discrete models is the optimal selection of the number of time periods that needs to be employed. A highly discretized grid results to better quality solutions but in in computationally intractable models, since the number of variables is highly increased. An advantage of discrete-time models is their ability of monitoring mass balances, inventory and backlog levels, as well as the availability and consumption of utilities without introducing nonlinearity constraints. Moreover, time-dependent utility-pricing and holding and backlog costs can be linearly modelled, while integration with higher planning levels is straightforward (Maravelias and Sung, 2009). In continuous models, the horizon is subdivided into a fixed number of periods of variable length, which is defined as part of the optimization procedure. Both single, common and multiple, unit-specific time frames have been successfully employed to continuous-time models. Continuous formulations can mitigate some of the computational issues associated with discrete-time models, since fewer variables, are required for same scheduling problem. Recently, Lee and Maravelias (2018, 2020), proposed a general framework, combining advantages of both discrete and continuous-time representations. The various time representations are also depicted in Figure 1.4.

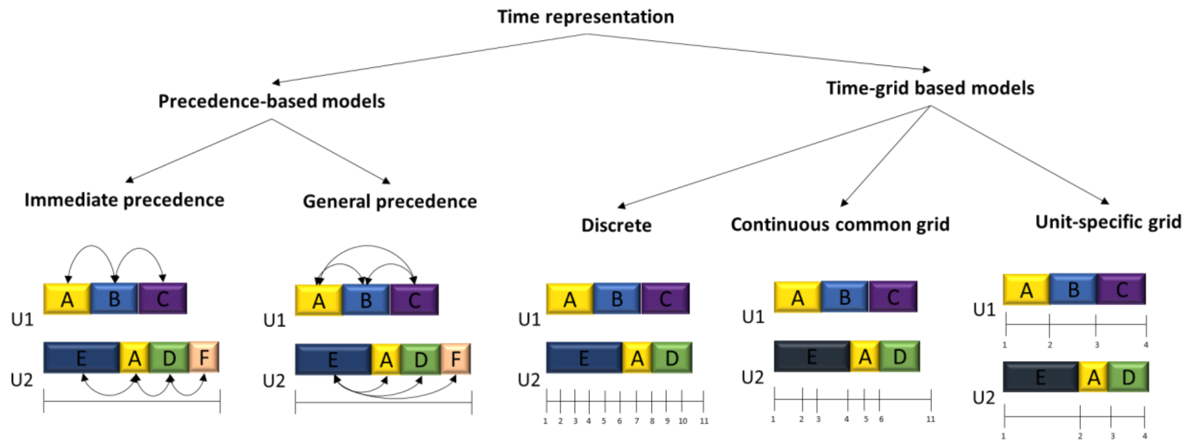

Figure 1.4 Categorisation of modelling approaches based on time representation

In the next subsections we demonstrate the basic research contributions in the scheduling optimization. More specifically, we present an overview of the models based on the problems they are used for and we analyse the basic constraints and variables of representative models. Further details on the different mathematical models for production scheduling can be found in the excellent reviews of (Méndez et al., 2006), Harjunkoski et al., (2014) and Georgiadis et al., (2019a).

1.2.5 Models for network production environments

In network environments batches do not maintain their identity, since mixing and splitting of batches is allowed. Hence, the problem the majority of the proposed scheduling models are based on either the STN or the RTN process representation (batch-based approaches). Moreover, the complexity of the production arrangement, with tasks consuming or producing multiple materials and materials being processed in different tasks and units, requires the proper monitoring of material balances, status of units and utility and inventory levels. Therefore, most of the proposed formulations rely on time-grid based approaches.

The introduction of the discrete STN and RTN models by Kondili, E., Pantelides, C. and Sargent, (1993), and Pantelides, (1994), emerged a plethora of modelling formulation. Mockus and Reklaitis, (1997) were the first to propose a continuous-time formulation based on the STN formulation and exploiting its generality. A common resource grid is used, with the timing of the grid points ("event orders" in their terminology)

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determined by the optimization. The model is a MINLP, which may be simplified to a mixed integer bilinear problem by linearizing terms involving binary variables, which is solved using an outer-approximation algorithm. Zhang and Sargent, (1996,1998), presented a continuous time formulation based on the RTN representation for both batch and continuous operations, with the possibility of batch size-dependent processing times for batch operations. Again, the interval durations are determined as part of the optimization. A MINLP model ensues; this is solved using a local linearization procedure combined with what is effectively a column generation algorithm.

One of the major disadvantages of the first models developed based on the continuous STN and RTN mathematical frameworks was the large optimality gap. This issue was addressed by Schilling and Pantelides, (1996). They developed a hybrid branch-and-bound solution procedure which branches in the space of the interval durations as well as in the space of the integer variables. A relaxation of Schilling's formulation (Schilling and Pantelides, 1996), has been proposed by Castro et al., (2001). Their model is less degenerate since it allows tasks to last longer than the actual processing time. Therefore, smaller CPU time is required. Castro et al., (2004) further improved this formulation in, allowing the optimization of continuous processes. A novel continuous STN-based formulation was introduced by Giannelos and Georgiadis, (2002). They utilized a non-uniform time grid, that eliminates any unnecessary time events, thus leading to small MILP models. Maravelias and Grossmann, (2003), suggested a general continuous STN-model that accounts for various processing characteristics such as, different storage policies, shared storage, changeover times and variable batch sizes. Another well-known MILP model was proposed by Sundaramoorthy and Karimi, (2005). The model is based on a continuous-time representation with synchronous slots, while a novel idea of several balances (resource, time, masses etc.) introduced.

The concept of multiple unit-specific time grids was first proposed by Ierapetritou and Floudas, (1998). This approach decouples the task events from the unit events, thus less slots are required. As a result, smaller MILP models are generated, leading to a significant decrease in computational effort. Multiple works have been proposed ever since, improving the computational characteristics and expanding the scope of the initial formulation (Janak et al., 2006).

Velez and Maravelias, (2013), were the first to introduce the concept of multiple, non-uniform discrete time grids. The multiple grids can be unit-, task- and material-specific. The same authors extended this work with the consideration of general resources and characteristics like changeovers and intermediate storages (Velez et al., 2017). It should be noted that while these formulations were initially proposed for network facilities, they can be also used for the scheduling of sequential environments.

1.2.6 Models for sequential production environments

Scheduling problems of sequential environments do not share the same complexity, in terms of problem representation, with the ones encountered in network environments. Therefore, both precedence-based and time-grid based approaches can be employed. Each of these approaches display specific advantages and drawbacks. On the one hand precedence-based models generate smaller, more intuitive models that provide high quality solutions, on the other hand time-grid based models are usually tighter and computationally superior. As a result, a great variety of models have been proposed to address sequential production environments.

One of the most important time-grid based models was proposed by Pinto and Grossmann, (1998). An MILP model has been developed for the minimization of earliness of orders for a multiproduct plant with multiple production units at each stage. The representation of time is achieved via two types of individual time grids: one for production units and one for orders. (Castro and Grossmann, 2005)proposed an MILP model, for the scheduling problem of multistage multiproduct plants, based on a non-uniform time grid representation. The formulation has been tested on various objectives e.g., minimization of makespan, total cost and total earliness and compared it with other known formulations. It is concluded that the efficiency of the model is highly depended on the objective and the problem features.

Maravelias and co-workers thoroughly investigated the employment of discrete-time models in sequential environments. Sundaramoorthy et al., (2009) proposed a discrete time model to integrate utility constraints for the scheduling problem of multistage batch processes. Merchan and Maravelias, (2016), proposed two novel formulations, based on the STN and RTN representation. Furthermore, they introduced tightening

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constraints that allowed for significant computational enhancements. Recently, Lee and Lee and Maravelias, (2017), presented two new MILP models for scheduling in multipurpose environments using network representations. Interestingly, states and tasks were defined based on batches instead of materials, making possible the consideration of material handling constraints in sequential production environments. The authors displayed the potential of the proposed models by incorporating important process features, such as time-varying data and limited shared resources, and by solving medium-size problem instances to optimality.

The concept of precedence has been extensively studied by the PSE community. Numerous unit-specific immediate (Cerdá et al., 1997), immediate (Méndez et al., 2000a) and general precedence (Méndez and Cerdá, (2002a), models have been proposed for scheduling problems in sequential environments. In initial studies the batches to be scheduled was predefined and constituted an input data, however later contributions suggested models for the simultaneous batching and scheduling problem (Cerdá et al., 2020; Kopanos et al., 2011, 2010b). Méndez et al. (2000) initially proposed the idea of precedence-based models, while Gupta and Karimi (2003) considered the impact of big-M constraints on the solution times and the overall performance of the model. The scheduling problem of a semi-continuous process of a yoghurt facility has been considered by Kopanos, Puigjaner, and Georgiadis (2010). A general-precedence MILP model has been presented for the scheduling of packing stage, while efficient mass balance constraints are imposed on batch stages to ensure the feasibility of generated schedules. A rescheduling approach, based on the previous MILP model has also been applied in a dairy industry by Georgiadis et al. (2019). Liu, Pinto, and Papageorgiou (2010), integrated travelling salesman problem (TSP) constraints in a precedence-based MILP model for the scheduling problem of single-stage batch plants. Recently, Cerdá, Cafaro, and Cafaro (2020) considered the scheduling problem of multistage bath plants with intermediate storage vessels. A general precedence MILP was proposed including batch sizing and new capacity constraints, to allow batch mixing and splitting.

1.2.7 Scheduling in make-and-pack industries

Current real-world industrial facilities include hundreds of different final products in flexible facilities operating under several tight design and operational constraints.

(Georgiadis et al., 2019a). Thus, several companies from various industrial sectors, have adopted flexible make-and-pack production processes. Production facilities used for such processes consist of a making stage and a pack stage. Depending on the shelf-life duration, they can be further categorized to durable goods (such as detergents) and nondurable (e.g. beverages). One category of the main consumer goods is the Fast-Moving Consumer Goods (FMCG), which are characterized by frequent purchases, rapid consumption and low prices.

Méndez and Cerdá (2002a), developed a general-precedence MILP model for the planning and scheduling of multiproduct make-and-pack continuous processes. The model includes lot-sizing, timing and sequencing constraints. Intermediate storage limitations are taken into account by introducing efficient mass balance constraints, without relying on concept of time-slots or event points. Méndez and Cerdá (2002b) proposed a general precedence-based MILP model for a make-to stock production facility. Unlimited storage capacity has been assumed for both intermediate and final products. Giannelos and Georgiadis, (2003), proposed a slot-based, MILP mathematical framework for the planning and scheduling of continuous processes. The mathematical framework is based on the STN representation and includes efficient intermediate storage constraints. The formulation was tested on a medium-size industrial consumer goods manufacturing process, considering cases with up to 35 final products and 5 packing lines. Feasible schedules are generated within a 5–10% integrality gap.

Janak, Lin, and Floudas (2004) proposed a continuous-time MILP for the scheduling of batch processes. The model is based on the STN representation using the idea of event time points. Günther, Grunow, and Neuhaus (2006) presented two different approaches for the production planning and scheduling problem of a hair dyes industry, by introducing the concept of block planning. Castro, Westerlund, and Forssell (2009) proposed an RTN-based MILP framework considering the scheduling problem of a tissue paper mill. The generation of byproduct waste has been efficiently taken into account by introducing novel recycling policies. Elzakker et al., (2012), presented a problem-specific model for the short-term scheduling problem, considering a Fast-Moving Consumer Goods (FMCG) industry. An algorithm based on a unit-specific, continuous time interval MILP model is proposed. Dedicated time intervals to specific product types are adapted to decrease the computational time. In order to assess the

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efficiency and the applicability of the proposed formulation ten industrial case studies are considered, as provided by Unilever, related to an ice cream production process. Optimal schedules have been generated for problem instance of up to 73 batches of 8 products allocated to six storage tanks and two packing lines within 170s. The time-horizon under consideration was 120 hours. The production scheduling problem of an ice cream facility has also tackled by Kopanos et al., (2012). A real-life case study of 8 final ice cream products, 2 packing lines and 6 aging vessels is introduced. The simultaneous optimization of all processing stages is achieved, and 50 problem instances are optimally solved. An MILP-based decomposition strategy is proposed to handle scheduling problems of large scale food process industries. High quality solutions were generated for larger cases of up to 24 final products utilizing the proposed decomposition technique.

An MILP-based hybrid method for a large scale consumer goods case study, has been developed by Baumann and Trautmann (2014). According to this approach, a subset of the final operations was scheduled iteratively, via the solution of a general-precedence MILP model (Baumann and Trautmann, 2013). Medium-sized problem instances were optimally solved within short CPU times. Aguirre, Liu, and Papageorgiou (2017) introduced a decomposition algorithm based on the concept of the rolling horizon approach, considering multistage continuous processes. The algorithm is based on a general precedence MILP model, assuming unlimited intermediate storage capacity and same production sequence throughout all stages. Elekidis, Corominas, and Georgiadis (2019) presented two MILP-based solution strategies for the scheduling optimization of a real-life, large scale, consumer goods industries. The proposed approaches lead to significant productivity gains by reducing the total changeover time. Yfantis et al., (2019), presented a discrete-time, MILP-based decomposition algorithm for continuous make-and-pack production plants with a large intermediate buffer tank. Extending this approach, Klanke et al. (2020), integrated a precedence-based, pre-sorting MILP model to improve the obtained solutions. Georgiadis et al., (2020), studied the integrated sterilization and packing stage scheduling problem in a large-scale canned fish Spanish industry. An MILP based decomposition algorithm is utilized to tackle the high computational cost, as the products are inserted in an iterative way until the final schedule is generated. A general precedence model efficiently describes the batch (sterilization) and the continuous (packing) processes of the plant. Recently, Elekidis and Georgiadis, (2021), proposed a continuous-time, precedence-based MILP model for the scheduling optimization problem of multiproduct make-and-pack continuous processes, with intermediate storage facilities. A new set of binary variables is introduced to accurately handle material balances and prevent overloading of storage vessels, without requiring any type of time horizon discretization. New resource constraints related to the generation and recycling of byproduct waste are also proposed to improve the utilization of raw materials and minimize byproducts management costs.

1.3 Integration of planning and scheduling

Among the different decision levels, tactical planning and medium-term scheduling are strongly connected. Tactical production planning is mainly concerned with determining efficient production targets over time while considering capacity limitations, mass balances and other constraints. On the other hand, scheduling level decisions are mostly related to timing and sequencing decisions. Planning and scheduling are often confused since no distinct differentiation exists between them. However, it is generally accepted that planning determines the input of the scheduling problem in terms of production targets like order sizes, due dates and release dates. Additionally, batching/lot-sizing decisions can be made in the planning level, thus affecting the type of decisions that needs to be made in the scheduling level. In that case batching/lot-sizing decisions are pre-defined, and the scheduling decisions include only unit to task assignment, sequencing and timing of tasks.

Despite the strong demand fluctuations, it is imperative that facilities satisfy the customer’s demand. Thus, equipment capacity must be fully utilized, while production targets must also be feasible. To address this challenge, scheduling level decisions can be integrated into planning models to enhance accuracy and to guarantee the feasibility of the generated solutions (Maravelias and Sung, 2009).

Taking this consideration into account, a plethora of mathematical frameworks have been proposed for the integrated planning and scheduling problem. The major modelling approaches for the integration of planning and scheduling decisions are presented in detail by Maravelias and Sung, (2009). Although earlier approaches have focused on developing monolithic planning and scheduling MILP formulations that include detailed scheduling constraints, this endeavor was soon abandoned since it results in computationally intractable models when the time horizon extends to several weeks or more months (Maravelias and Sung, 2009).

1.3.1 Planning and scheduling using monolithic approaches

The majority of monolithic approaches mainly focus on scheduling problems while considering medium-term planning decisions, such as lot or batch sizing. Papageorgiou and Pantelides (1996), proposed an integrated campaign planning and scheduling MILP model for semicontinuous process industries. To reduce the complexity of the problem, the idea of cyclic scheduling have been considered. Méndez and Cerdá, (2002), developed a general-precedence MILP model for making scheduling and lot-sizing decisions of multiproduct, continuous processes. Novel mass balance constraints are introduced for the storage of intermediate products without utilizing any type of time horizon discretization. Giannelos and Georgiadis, (2003) have proposed an MILP model for the medium-term scheduling of continuous processes, considering also lot-sizing decisions. The simultaneous batching and scheduling of single-stage batch plants has been addressed by Castro et al., (2008). Two MILP formulations have been developed based on either global precedence variables or multiple time grids. The batching and scheduling problem has also been considered in multi-stage processes by Sundaramoorthy et al., (2009). Kopanos et al., (2010), considered the medium-term planning and scheduling problem of a yoghurt facility. A general-precedence MILP model has been proposed for the scheduling of packing stage, while lot-sizing decisions are made for a weekly time horizon. Recently, Cerdá et al., (2020), proposed a novel general-precedence MILP model for the scheduling of multi-stage batch plants. The model considers batch sizing decisions, while new capacity constraints are also included to allow for batch mixing and splitting.

Although monolithic approaches can be efficiently applied in small or medium-sized problems, only a limited number of them are able to solve large-scale industrial problems when the time horizon extends to several weeks or months. Thus, many research works have focused on developing hybrid mathematical frameworks by combining MILP models with heuristic methods or hierarchical decomposition

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techniques (Georgiadis et al., 2019a). Günther et al., (2006), incorporated the concept of block planning into an MILP model to solve a real-life production planning and scheduling problem of a hair dyes industry. Bilgen et al., (2014), proposed a hybrid method based on an MILP model and a simulation algorithm for the production and distribution planning in the soft drink industry. The integrated lot-sizing and scheduling problem of a brewery industry has been addressed by Baldo et al., (2014). In order to solve real-life problem instances, a set of efficient heuristic rules are used in parallel with an MILP model. The same problem has also been solved by Georgiadis et al., (2021). Large-scale problem instances can be efficiently solved in acceptable by the industry computational times, using an MILP-based solution strategy that consists of a constructive and an improvement step.

1.3.2 Planning and scheduling using the rolling horizon framework

Hierarchical decomposition techniques have also been widely used for long-term planning and scheduling problems. In hierarchical methods, a set of high-level decisions, such as production targets, are defined at the planning level. Planning level decisions constitute the main input of the lower-level scheduling problem that is solved to obtain a detailed optimal solution. Among various hierarchical approaches, the idea of the rolling horizon has been widely considered by research community to solve long-term planning and scheduling problems. The concept of rolling horizon is based on solving a detailed scheduling formulation only for a few early periods, while aggregated planning models are solved for the rest of the time horizon under consideration. Decisions related to the early periods are exact and thus directly implemented, while long-term planning decisions can be updated as the time horizon rolls. Dimitriadis et al., (1997), introduced both forward and backward rolling horizon approaches for medium-term planning and scheduling of multipurpose plants. According to the forward rolling horizon approach, successive scheduling periods are solved sequentially in detail. On the contrary, in backwards rolling horizon framework, the last time period constitutes the first scheduling period that is being solved. Erdirik-Dogan and Grossmann, (2007), addressed the production planning of parallel batch reactors using an MILP-based rolling horizon scheme. Sequencing of tasks is accurately taken into account at the planning level by integrating a set of travelling salesman constraints. Verderame and

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Floudas, (2008) developed an MILP-based rolling horizon framework for the integrated operational planning and medium-term scheduling of multipurpose batch plants that produce both made-to-order and made-to-stock products. A feedback loop is also incorporated into the rolling horizon framework to obtain more accurate solutions,. Li and Ierapetritou, (2010) proposed a rolling horizon approach for the integrated planning and scheduling of multipurpose facilities. To enhance the efficiency of the modeling framework, production capacity information is considered in the planning model by using the method of parametric programming.

1.3.3 Planning and scheduling under uncertainty

A significant challenge within the field of integrated planning and scheduling is the consideration of uncertainty. Various types of uncertainty can be examined. For example, customer demand, product prices, demand due times, and raw materials availability can be modelled as uncertain parameters. As it is described above, the integration of planning and scheduling is typically a challenging problem. Hence, the consideration of uncertainty causes a further increase in the complexity of the problem. However, several industrial cases have proven that the assessment of uncertainty within planning and scheduling can have a massive impact on the profitability of a plant as different objectives of a company can be compromised (Verderame et al., 2010). An important decision is related to which uncertainties must take into account at the planning and the scheduling level. Furthermore, uncertainty can be classified as continuous, and discrete distributions. Several techniques can be utilized in order to examine different types of uncertainty. A detailed description of the different approaches for integrated planning and scheduling under uncertainty is presented by Verderame et al., (2010).

Among them, rolling horizon approaches have been widely proposed. Wu and Ierapetritou, (2007), proposed a multi-stage stochastic rolling horizon framework for the integrated planning and scheduling under demand uncertainty. The time horizon has been discretized into three stages with increasing levels of uncertainty. An efficient feedback loop was also integrated into the modelling framework to converge the planning and scheduling production targets. Verderame and Floudas, (2010), addressed both demand and processing time uncertainty by developing a rolling horizon

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modelling framework for the operational planning and scheduling of multipurpose batch plants. The proposed framework allows for a two-way interaction between planning and scheduling decision levels through a feedback loop.

Usually, methods for modelling uncertainty, such as stochastic programming, can obtain a solution that performs optimally over a given set of scenarios. These methodologies are very efficient when the decision-maker is risk-neutral since they focus on maximizing the potential gains regardless of the risk. This approach is however myopic since a risk-averse decision-maker would prefer to avoid the opportunity for a significant gain in favor of safety. Taking this into account, the importance of considering risk measures in the integrated planning and scheduling model can be realized. In particular, risk measures such as Value-at-Risk (VaR) and Conditional Value-at-Risk (CVaR) can constitute a valuable method to control risk in the decision-making process (Cardoso et al., 2016; Vieira et al., 2020). Both VaR and CVaR evaluate the risk of a variable under a certain degree of confidence and aim to guard against the adverse realization of uncertain parameters. Verderame and Floudas, (2010b) considered the problem of operational planning under due date and demand uncertainty of multiproduct batch plants, by developing a novel MILP modelling framework based on the CVaR measure. A sample average approximation has also been utilized to maintain computational tractability when a large set of scenarios is considered. Vieira et al., (2020) proposed a two-stage MILP model for the integrated retrofit design and scheduling of multipurpose batch plants. The Conditional Value at Risk (CVaR) measure was incorporated into the mathematical model to evaluate the risk of experiencing both downside losses and upside gains.

Making realistic decisions while assessing uncertainty may require the consideration of numerous scenarios. This issue can significantly increase the size of the optimization problem, making it very hard to solve. To overcome this limitation, various scenario reduction frameworks have been proposed. Karuppiah et al., (2010) proposed a heuristic method for the scenario reduction of discrete distributions. Li and Floudas, (2014), also proposed an MILP model for the scenario reduction problem. To enhance the quality of the solution, the proposed MILP model takes into account both input and output space of the initial distribution.

1.3.4 Planning and scheduling in the pharmaceutical industry

Among different industrial sectors pharmaceutical industry is composed of many challenging planning and scheduling problems possessing both industrial and academic significance (Shah, 2004; Marques et al., 2020; Sarkis et al., 2021;). Planning of clinical trials is one of the most significant and complex problems in the pharmaceutical industry, since it lasts several years and costs a tremendous amount of money. A schematic representation of drug discovery process is depicted in Figure 1.5. Gatica et al., (2003), considered the pharmaceutical capacity planning problem under clinical trials uncertainty. Four clinical trial outcomes (high success, target success, low success, failure) are taken into account for each product, using a multi-scenario MILP model. A risk measure has also been formulated to evaluate risk and potential returns of each option. Levis and Papageorgiou, (2004), presented an aggregated, multi-site, planning model for pharmaceutical industries in an attempt to integrate drug portfolio management and supply chain design problems. The proposed modelling approach aims to maximize the patent lifetime of drugs and the total profit. Colvin and Maravelias, (2008), also addressed the clinical trial planning in new drug development by solving a multi-stage stochastic MILP model. To address larger problem instances a benders decomposition algorithm has been proposed by Sundaramoorthy et al., (2012).

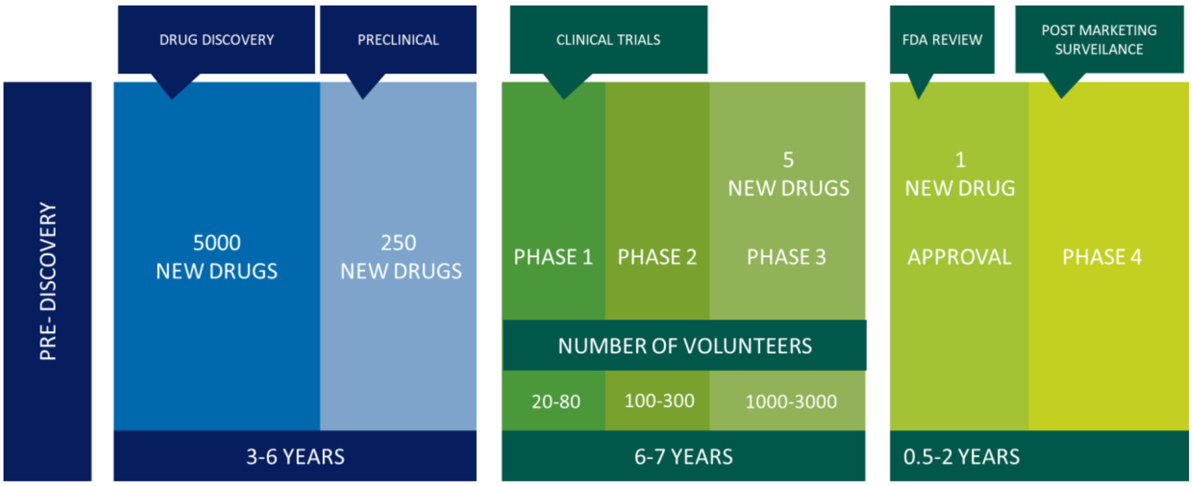

Figure 1.5 Schematic representation of the drug discovery process.

Production of both active pharmaceutical ingredients (APIs) and final products is a complex task, as the process industries must comply with strict safety guidelines, imposed by regulatory agencies, such as Food and Drug Administration (FDA). Hence, several research works have been focused on the scheduling optimization of pharmaceutical industries. Stefansson et al., (2006) suggested two MILP models for the short-term scheduling of pharmaceutical industries. A temporal decomposition is utilized, as the production stages are scheduled sequentially to reduce the complexity of the initial problem. The integrated supply chain planning and scheduling of pharmaceutical industries has been addressed by Amaro and Barbosa-Póvoa, (2008). The two decision levels are solved sequentially, while the consideration of reverse product flows allows for further solution improvement. Castro et al., (2009) also addressed the scheduling problem of multi-stage batch pharmaceutical industries. To overcome the complexity of realistic problem instances, an RTN-based decomposition technique is proposed. The modelling framework allows for partial rescheduling decisions during each iteration to obtain nearly optimal schedules. An iterative decomposition algorithm has also been developed by Kopanos et al., (2010a), for the short-term scheduling of large scale, multi-stage, batch pharmaceutical industries. A general-precedence MILP model constitutes the main core of the algorithm that consists of two main steps. During the first step, a feasible solution is obtained. An improvement step is also incorporated to obtain good quality solutions. Stefansson et al., (2011), addressed the integrated planning and scheduling problem of secondary pharmaceutical industries. An MILP- based solution framework is proposed using a moving horizon approach to solve real-life problem instances. Sousa et al., (2011) considered the global supply chain planning of pharmaceutical companies. Two MILP-based decomposition algorithms was proposed to face the complexity of large problem instances that include production at primary and secondary sites and product distribution to markets. Vieira et al., (2016) proposed a continuous-time, RTN-based, MILP model for the campaign planning and scheduling of biopharmaceutical processes. The model includes key problem features, such as shelf life and batch mixing or splitting constraints. A model-based tool for the production and maintenance planning optimization in a biopharmaceutical industry has also been presented by Vieira et al., (2019).

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1.3.5 Contract Manufacturing Organizations in the Pharmaceutical Industry

During the last 20 years, due to the shortening of patent life periods and the intense competition, an increasing trend is noted for outsourcing activities in the pharmaceutical industry (Jarvis, 2007; Sarkis et al., 2021). One of the main advantages of outsourcing is that it allows large multinational companies to focus on their core competencies, such as drug discovery and marketing. Furthermore, since CMOs manufacture products for multiple customers, they benefit from economies of scale and can decrease individual costs regarding purchasing of raw material, production, and storage. Outsourcing allows multinational companies to focus on larger product portfolio without increasing capital expenses associated with the construction of new facilities (Johnson, 2005; Sarkis et al., 2021). Usually, value of drugs typically halves on patent expiry. After patent life the competition is more vigorous in the market due to the development of generic drugs. The typical life-cycle of pharmaceutical products is also illustrated by Figure 1.6. Hence, a contract can be offered to a CMO even before the final approval of a drug in order to take full advantage of the patent period. Furthermore, potential adverse effects can decrease significantly the value and the demand of new drugs. Under this uncertain environment CMOs has to optimally define the appropriate contract combination in order to maximize the profit margins and to ensure their viability.

Johnson, (2005), addressed the contract appraisal problem of Contract Manufacturing organizations under demand uncertainty in the fine chemicals industry. Based on the RTN representation, a modelling framework was introduced for the planning and scheduling of multipurpose network-based facilities. Due to the combinatorial nature of the problem, each contract combination and each scenario are solved independently, via a two-phase solution algorithm. The determination of the optimal contract mixture is made considering risk measures such as Value-at-Risk (VaR) and left-side mean absolute deviation.

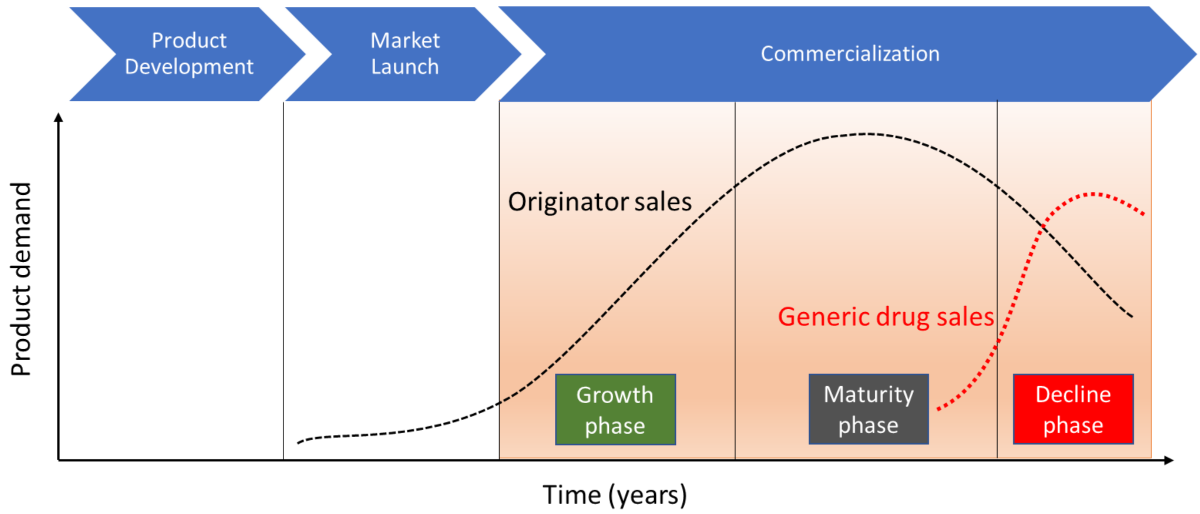

Figure 1.6 Demand of pharmaceutical products over time

To the best of our knowledge, there is no previous research work that considers the contract selection problem of CMOs under demand uncertainty in the secondary pharmaceutical industry in the open literature. Therefore, an optimization framework for the contract selection of CMOs is proposed in Section 4. Demand uncertainty is modelled via a set of independent scenarios for each contract. To enhance the solution accuracy, scheduling level decisions are explicitly taken into account. In particular, an MILP-based, rolling horizon framework is proposed for the integrated tactical planning and medium-term scheduling of multi-stage batch facilities. Risk measures such as Value-at-Risk (VaR) and Conditional Value-at-Risk (CVaR) are utilized to evaluate and mitigate risk while considering the optimal mixture of tendered contracts to accept. A scenario reduction MILP model is also utilized to solve large-scale problem instances with multiple scenarios.

1.4 Thesis Overview

This thesis is organized as follows:

In **chapter 2,** the optimal short-term scheduling of continuous process industries is addressed. Firstly, two precedence-based MILP models are proposed. Furthermore, two decomposition algorithms are presented to solve large-scale problem instances. The proposed optimization methods are applied to real-life industrial problems. More specifically, the optimal production scheduling of a continuous consumer goods

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industrial facility is considered. It is shown that both methods can provide near-optimal solutions in low CPU times. Comparing the obtained solution with the manually derived schedules by the production engineers, significant benefits are noticed in terms of changeover minimization and productivity improvement.

In **chapter 3,** the optimal scheduling of continuous make-and-pack processes with flexible intermediate storage vessels and byproducts recycling is addressed. The process structure under study is commonly met in several industrial sectors, such as food and beverages, specialty chamicals and consumer goods industries. Based on a continuous-time representation, a novel MILP model is proposed. The model relies on a new set of binary variables that enable the efficient consideration of mass balance constraints. Constraints related to byproduct recycle streams are also taken into account to enhance the general utilization of resources and reduce total waste. An MILP-based solution strategy is proposed to face complex problem instances. An industrially relevant scheduling problem is considered to evaluate the efficiency of the proposed modelling frameworks. Results show that the utilization of flexible storage equipment allows for better synchronization of production stages, while the consideration of byproduct constraints significantly reduces waste and raw material usage.

Chapter 4 investigates the optimal contract selection problem of Contract Manufacturing Organizations in the pharmaceutical industry under uncertainty. The problem is mainly focused on secondary pharmaceutical production. Hence, an integrated planning and scheduling modelling framework is presented for multistage batch facilities. The proposed MILP models are solved via a rolling horizon approach. A solution algorithm is introduced based on a set of discrete demand scenarios to model demand uncertainty considering risk metrics such as Value-at-Risk (VaR) and Conditional Value-at-Risk (CVaR). Results demonstrate that the developed modelling framework constitutes a systematic approach for the contract appraisal problem of Contract Manufacturing Organizations as it can provide the optimal contract mixture depending on the corresponding risk tolerance.

Chapter 5 provides a synopsis of the research outcomes of this thesis. Possible future research directions are also proposed.

2

Optimal Production Scheduling of Consumer Goods Industries

2.1 Introduction

This chapter considers the production scheduling of real-life consumer goods industries. In particular, we focus on continuous make-and-pack processes that constitute a typical production layout in fast-moving consumer goods industries (FMCGs), such as the production of detergents or soft drinks. Most of those industries usually consist of a processing stage that prepares the intermediate products based on a given recipe, followed by a packing stage. In continuous make-and-pack industries, the overall production rate is determined by the slowest production stage, which is typically the packing process. Despite the extensive scientific work on the subject of optimal production scheduling, these types of facilities were not sufficiently addressed, thus underlying a significant gap in the literature.

Furthermore, over the past 20 years, the literature illustrates a large number of scheduling models, which have been mostly applied to generic but relatively small or medium problem instances (Castro et al., 2009b; Cerda et al., 2002; Giannelos and Georgiadis, 2003; Kopanos et al., 2011). However, current real-world industrial applications include hundreds of different final products produced under several tight design and operating constraints (Castro et al., 2018; Harjunkoski et al., 2014). Therefore, only a few approaches have been used to solve large-scale industrial scheduling problems, in continuous process industries (Georgiadis et al., 2019a).

The main goal of the work, presented in this chapter, is to effectively fill this scientific gap, by proposing novel mathematical frameworks that can solve large-scale production scheduling problems for continuous processes. An immediate-precedence and a unit-specific general precedence-based MILP models are proposed that approach the problem at hand. The models focus on the packing stage, taking also into account constraints referring to the production/formulation stage, in order to ensure the generation of feasible production schedules. Constraints related to maintenance restrictions are also considered. Two MILP-based decomposition strategies are also proposed to solve realistic problem instances in acceptable computational times, as imposed by the industry.

In order to evaluate the efficiency of the proposed modelling frameworks, the scheduling of a real-life consumer goods industry is considered (Elekidis et al., 2019). More than 300 products can be produced continuously in parallel packing lines. The production process consists of the formulation/production and the packing stage. In the formulation stage, multiple intermediate products are produced, while in most cases, more than one final product can be produced from the same intermediate product in the packing stage. Each packing line is connected to its own production/formulation unit. Sequence-dependent changeovers take place in both stages. The changeover times differ among the various sequences, depending on the package size, the package color, the intermediate product etc. All changeovers, in the two stages, take place simultaneously and therefore, the most time-consuming changeover determines the total changeover time for a product sequence. In addition, due to technical plant restrictions in the formulation stage, the total number of intermediate products' changeovers should not exceed an upper limit. The short-term scheduling horizon of interest is one week, and both the packing and the formulation units are available 24 hours per day. Products' due dates are considered along with the necessary planned maintenance activities. The main objective of the plant is the minimization of total changeover time.

The applicability of the proposed approaches is illustrated by solving several real-life industrial problem instances in the consumer goods industry under consideration. Scheduling solutions have been validated by the industry and directly compared with schedules derived by the operators using simulation tools. Significant changeover time reductions are achieved, leading to improvements in the overall plant productivity. The proposed solution strategies also provide the basis of an automated tool that allows decision-makers to take quick and near-optimal scheduling decisions.

2.2 Problem Statement

The scheduling problem under consideration is inspired by a real-life, large-scale industrial plant, of a multi-national consumer goods corporation. More specifically, a large variety of fast-moving consumer goods (FMCG) is produced on a daily basis for different purposes. The packaged products are distributed to several countries and customer centers, depending on their specific features. More than 300 final liquid detergent SKUs are produced during a week via production campaigns, in order to satisfy customer demand. A plethora of raw materials and base liquids are transformed into intermediate products through a continuous production/formulation process. Intermediate items are packaged in several sizes and types. The high degree of diversification in the raw materials, enables the production of a huge variety of final products. The main production stages are illustrated in Figure 2.1.

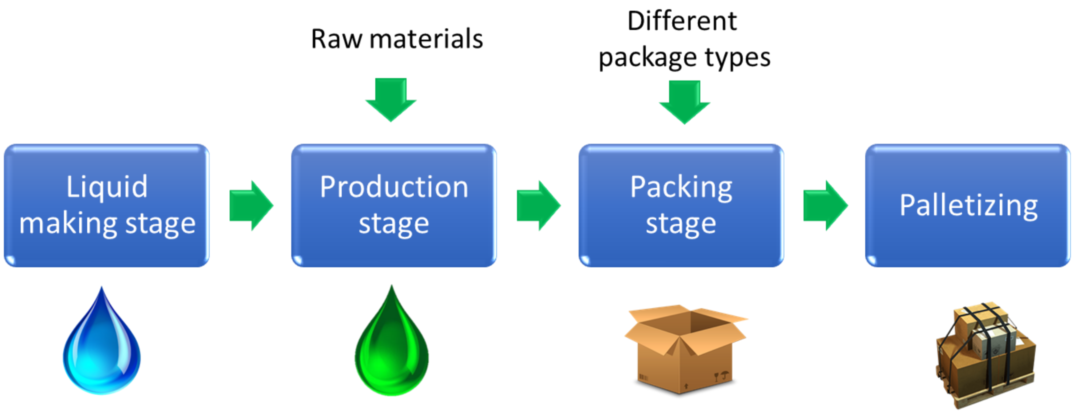

Figure 2.1 Plant production stages

According to the current plant layout, fully flexible product allocation is allowed in the production stage and each intermediate product can be produced in any of the available production units. Since the production stage is overdesigned, the related scheduling decisions do not need to be decided in detail. On the other hand, the packing stage consists of several non-identical packing lines. Underlying production policies often assign products to selected packing units. Both stages operate in a continuous mode. As there is no intermediate storage capacity between the two stages, intermediate products are transported directly to a set of parallel packing lines. Due to the lack of intermediate storage capacity and according to other design limitations, each production unit is strictly connected to only one packing line. The packing stage is described as the most time-consuming process and constitutes the main production bottleneck of the plant. The current plant layout is depicted on Figure 2.2.

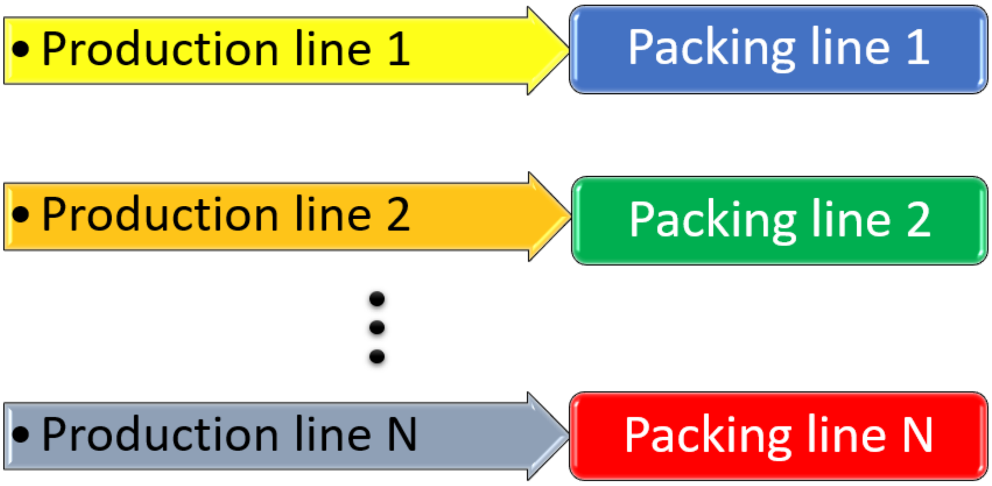

Figure 2.2 Plant overview – Current layout

Due to the wide range of raw materials, the different package types and sizes, the diverse kinds of labels, and other product-dependent features, a large number of changeovers take place in both stages, thus resulting in large production downtimes, higher usage of human resources and unnecessary energy consumption. Furthermore, frequent changes of raw materials, used in the formulation stage, lead to the generation and the accumulation of undesirable amounts of byproduct waste. The generated liquid waste is recycled, so that small amounts of it are reused into the next production campaigns without affecting the product's quality. The limited storage capacity of liquid waste imposes un upper bound on the total number of liquid changeovers on a daily basis. All changeovers take place simultaneously in the two stages and therefore, the most time-consuming changeover determines the total changeover time for a product sequence. Changeover times should be explicitly considered, as they constitute a key feature of the production process. The minimization of the total changeover time is the overarching target of the plant, as it significantly improves the plant's productivity, by decreasing the equipment idle time and generation of byproduct liquid waste in the production stage.

The short-term scheduling horizon of interest is one week (or less) and both the packing and the production units operate continuously 24 hours per day. Full demand satisfaction must be achieved, and strict due date constraints must be satisfied, since products have to be delivered on time to the customer's centers. Various planned maintenance activities take place as determined by the ERP system of the plant. Once a product campaign starts, it must be carried out until completion without interruption, as the splitting of product orders is not allowed due to the underlying industrial policy. One of the main challenges faced by the planning engineers, is the highly volatile demand, which makes the production environment extremely dynamic. Frequent, late-order arrivals, or sudden order cancelations, impose the need of several modifications in the initial production schedule on a daily basis. Consequently, there is a significant need for the quick generation of good quality schedules, that will assist the production engineers in their effort to develop rigorous scheduling plans under dynamic demand changes.

In general, the large number of products and the high production flexibility increase the complexity of the scheduling problem significantly. Although the problem under study is focused mainly on the scheduling of the packing stage, which constitutes the main production bottleneck, all necessary technical and operational constraints, related to the production stage, are also considered. Thus, the generation of infeasible production schedules is avoided.

Since the plant operates continuously 24 hours per day, the main objective function under consideration is the minimization of the total changeover time. However, other alternative objectives, such as the minimization of makespan, could also be considered, depending on the prevailing needs of the plant.

The problem under consideration can be formally defined as follows:

Given:

- The time horizon of interest
- A set of products
- A set of parallel packing lines/units

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- A multidimensional set describing if a packing line is capable to produce the production order.
- The packing units availability
- Product due dates and demand
- Packing rates of units
- The processing time of each product order
- The changeover time, expressing the necessary transition time between the production of two consecutive orders, in each packing unit. The changeover time of final products is precalculated, based on the products' package types and sizes, the package color, the diverse kinds of labels, the related intermediate products and other product's features.
- An upper limit of intermediate products' changeovers. Due to the limited plant's resources and the liquid waste generation, this upper limit is determined by the scheduling operators.
- The time window, defining if the completion of an order has to take place during a specific time slot. In that case the related starting time has to be greater than a lower limit.

Determine:

- The allocation of products to packing lines,
- The sequencing of product orders in every packing line,
- The completion time of each production order,

So as:

Optimize a given objective function.

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2.3 Mathematical frameworks

In this section two MILP models are proposed, to address the real-life industrial scheduling problem, described above. Both formulations utilize the concept of the precedence variables. The first mathematical framework is based on the immediate precedence sequence of product orders in parallel units (Kopanos et al., 2011), while in the second one, the idea of global sequencing variables is also adopted, leading to a unit-specific general precedence model (Kopanos et al., 2010a).

It is known that general precedence scheduling models, can be usually solved faster, as they rely on a smaller number of variables. It has been shown that general precedence-based models are generally more efficient compared to immediate precedence models (Méndez et al., 2006). However, sequence-dependent objectives, such as the changeover minimization, cannot be considered without the incorporation of immediate precedence variables. The proposed MILP-based models, described in the next two subsections, can be solved directly, or they can provide the core of MILP-based decomposition strategies, described in detail in the section 2.4.

2.3.1 Immediate precedence single-stage MILP-model

In this subsection, an immediate-precedence, single-stage model, of parallel units is described. The model is inspired by an immediate precedence MILP model developed by Kopanos et al., (2011), for the integrated planning and scheduling problem of parallel continuous processes. Instead of using the idea of the mixed discrete-continuous time representation, the proposed MILP model relies on a unified time horizon. Furthermore, efficient big-M values have been investigated in order to improve the overall computational performance of the model. Except from the typical assignment, timing and sequencing constraints, problem-specific constraints have also been included. Henceforth, we will also refer to this immediate precedence MILP model as IPM. A detailed description of the MILP model is presented below, as follows:

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Assignment constraints

$$\sum_{j \in i_j} Y_{i,j} = 1 \quad \forall i \tag{2.1}$$

Constraints (2.1) guarantee that each product order is assigned to one unit $j \in J_i$.

Product orders sequencing constraints

$$\sum_{i',\, i' \neq i} XX_{i',i,j} \leq Y_{i,j} \quad \forall i, j \in J_i \tag{2.2}$$

$$\sum_{i',\, i' \neq i} XX_{i,i',j} \leq Y_{i,j} \quad \forall i, j \in J_i \tag{2.3}$$

$$\sum_{i, i \in J_i} \sum_{i',\, i' \neq i, i' \in J_i} XX_{i',i,j} + 1 = \sum_{i, i \in J_i} Y_{i,j} \quad \forall j \tag{2.4}$$

We introduce the binary variable $XX_{i',i,j}$ to define the local immediate precedence between two products i and i'. The binary variable takes the value 1, only if a product order i' is processed immediately after production order i in unit $j \in J$. Constraints (2.2) and (2.3) ensure that, if production order $i \in I$ is allocated to packing line $j \in J$, at most one production order is processed before and after it, respectively. Apparently, in case that the production order is processed first or last then it has no predecessor or successor. According to constraint (2.4), the total number of sequences in a packing unit $j \in J$ has to be equal to the total number of produced orders minus one.

Time window constraints

$$C_i - T_i \geq Lower_i \quad \forall i, window_i = 1 \tag{2.5}$$

According to the underlying inventory constraints of the plant, some products have to be produced, during a strictly defined time window. These production campaign cannot start before a lower time limit, $Lower_i$, without also exceeding their related due dates

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$DDATE_i$. The parameter $window_i$ takes the value 1, only if a production order has to be produced during a specific time window as the value $Lower_i$ is predefined according to the industry's needs. Otherwise, the $window_i$ parameter takes the value 0 and the parameter $Lower_i$ is also equal to 0.

Timing constraints

$$C_{i'} \geq C_i + T_{i'} + XX_{i,i',j} changeover_{i,i'} - DDATE_i(1 - XX_{i,i',j}) \quad (2.6)$$

$$\forall i, i' \neq i, j \in \left(i_j \cap i'_j\right)$$

According to the big-M constraints (2.6), the completion time $C_{i'}$ of a product order *i'* has to be greater that the completion time of whichever product *i* is produced beforehand at the same unit, plus the processing time $T_{i'}$ and the corresponding changeover time, expressed by the parameter $changeover_{i,i'}$, only if the binary variable $XX_{i,i',j}$, is equal to 1. Constraint (2.6) also ensures the avoidance of sequence subcycles in the final schedule.

$$C_{i'} \leq C_i + T_{i'} + XX_{i,i',j} changeover_{i,i'} + (DDATE_{i'} - T_{i'})(1 - XX_{i,i',j}) \quad (2.7)$$

$$\forall i, i' \neq i, j \in \left(i_j \cap i'_j\right), window_i \neq 1$$

Constraints (2.7) enforces the completion time $C_{i'}$ of a product order *i'* to be smaller or equal to the sum of the completion time C_i of product *i* produced prior to order *i'* at the same unit, the processing time $T_{i'}$, and the changeover time, $changeover_{i,i'}$. Constraints (2.7) has to be taken into account if the minimization of changeover times constitutes the objective function, since otherwise unnecessary idle times are observed in the generated schedules. The production orders, produced in a strict time window, ($window_i = 1$), are excluded from constraints (2.7), because infeasible production schedules may be generated.

The selection of the big-M value has a crucial impact on the computational complexity (Gupta and Karimi, 2003). Increased big-M values relax the domain of the continuous

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variables. A same pattern appears also in the solution of the MILP problem. Hence, the computational time required, for achieving the global optimum and reducing the relative gap between the relaxed and the best integer solution, is getting prohibitively high (Aguirre et al., 2017). In the proposed MILP formulation efficient big-M values have been chosen, for the purpose of reducing the computational time and providing more efficient mathematical models.

In particular, according to constraints (2.6), the big-M value is equal to the $DDATE_i$. Since variable C_i is smaller or equal than the parameter $DDATE_i$ and the binary variable $XX_{i,i',j}$ is equal to 0, the constraint expresses that $C_{i'}$ should be greater than the related processing time, $T_{i'}$, minus a small number (equal to $C_i - DDATE_i$), which is significant smaller than the usually used value of the time horizon under consideration.

The same concept is also applied in constraint (2.7), as the big-M value is equal to, $(DDATE_{i'} - T_{i'})$. When the binary variable $XX_{i,i',j}$ is equal to 0, the constraint expresses that the $C_{i'}$ should be smaller than the related due date time ($DDATE_{i'}$) plus the value of the variable C_i. The proposed value is also significant smaller, than the commonly utilized value, equal to the scheduling time horizon of interest.

Formula card constraints (Production stage constraints)

$$\sum_{j} \sum_{i, i \in J_i} \sum_{\substack{i', i' \neq i, i' \in J_i \\ formula_i \neq formula_{i'}}} (XX_{i',i,j}) \leq Limit \tag{2.8}$$

Constraint (2.8) are referred to the production/ formulation stage of the facility. As it was described above, several changeovers take place among the production of different intermediate products due to cleaning or other activities. Furthermore, a significant amount of byproduct waste material is generated, which can be partially reused into the next product campaigns. Due to the lack of the necessary resources and the limited storage capacity of the occurred waste the total changeovers related to the intermediate products with different recipe, $formula_i$, should not exceed an upper limit, $Limit$.

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Due date constraints

$$C_i \leq DDATE_i \quad \forall i \tag{2.9}$$

Constraints (2.9) forces the completion time of a production order C_i to be lower or equal than its deadline, expressed by the parameter $DDATE_i$.

Objective Functions

a) Minimization of production makespan

$$\min C_{max} \geq C_i \qquad \forall i \tag{2.10}$$

b) Minimization of total changeover time

$$\min CT = \sum_{j} \sum_{i, i \in J_i} \sum_{i', i' \neq i, i' \in J_i} XX_{i,i',j} changeover_{i,i'} \tag{2.11}$$

Objective (2.10) expresses the minimization of the total production makespan, C_{max}, while constraint (2.11) expresses the minimization of changeovers and unnecessary idle times.

Planned maintenance activities are also considered. Each maintenance task is represented by a dummy product order, which is inserted into the production schedule, by fixing their allocation and their completion variables $Y_{i,j}$ and C_i. These dummy product orders have also to be processed during a time window and therefore their related parameter $window_i$ is equal to 1.

2.3.2 Unit-specific General Precedence Single-Stage MILP Model

A single stage, unit-specific general precedence MILP model of parallel units is proposed here. It is based on an extension of a unit-specific precedence framework developed by Kopanos et al., (2012). A continuous time representation has been utilized and problem-specific constraints have been added. As the main objective under consideration is the minimization of the total changeover time, timing constraints (2.15) have been

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included, in order to avoid the generation of unnecessary idle times in the package units. Efficient big-M values have been used in the timing constraints, in order to improve the performance of the model. Furthermore, constraints related to the formulation/production stage of the plant, as well as due date constraints have also been adapted into the MILP model. Henceforth, we will refer to this MILP model as USGP. Constraints are described in detail, according to the type of decision (e.g., assignment, timing, sequencing, etc.), as follows:

Assignment constraints

$$\sum_{j \in i_j} Y_{i,j} = 1 \quad \forall i \tag{2.12}$$

Constraints (2.12) guarantee that each product order is processed in just one unit $j \in J_i$

Timing and sequencing constraints

$$X_{i',i,j} + X_{i,i',j} + 1 \geq Y_{i',j} + Y_{i,j} \qquad \forall i, i' > i, j \in \left(i_j \cap i'_j\right) \tag{2.13}$$

$$C_{i'} \geq C_i + T_{i'} + XX_{i,i',j} changeover_{i,i'} - DDATE_i\left(1 - X_{i,i',j}\right)$$
$$\forall i, i' \neq i, j \in \left(i_j \cap i'_j\right) \tag{2.14}$$

$$C_{i'} \leq C_i + T_{i'} + XX_{i,i',j} changeover_{i,i'} - (DDATE_{i'} - T_{i'})(1 - X_{i,i',j})$$
$$\forall i, i' \neq i, j \in \left(i_j \cap i'_j\right), window_i \neq 1 \tag{2.15}$$

$$2(X_{i',i,j} + X_{i,i',j}) \leq Y_{i',j} + Y_{i,j} \qquad \forall i, i' > i, j \in \left(i_j \cap i'_j\right) \tag{2.16}$$

Constraints (2.13) - (2.16) provide the relative sequencing of product orders. The big-M constraints (2.14) and (2.15) impose the completion time $C_{i'}$ of a product order *i'* to be greater that the completion time and the processing time $T_{i'}$ of whichever product *i* is produced beforehand at the same unit, and greater than the changeover time, $changeover_{i,i'}$, only if the binary variable $X_{i,i',j}$ is active. The binary variable $X_{i,i',j}$ is active only if product *i'* is produced after product *i.* The big-M values are defined, as described in subsection 2.3.1 for the timing equations (2.6) and (2.7). Constraints (2.15) ensures the avoidance of unnecessary idle times. Constraints (2.13) and (2.16) state that when two products are produced at the same unit, only one global sequencing binary variable has to be active and when one of the binary variable $X_{i',i,j}$ and $X_{i,i',j}$ is active, at least one of the $Y_{i,j}$ and $Y_{i',j}$ has to be active as well.

Immediate precedence constraints

$$Z_{i,i',j} + XX_{i,i',j} \geq X_{i,i',j} \quad \forall i, i', j \in (i_j \cap i'_j) \tag{2.17}$$

$$Z_{i,i',j} = \sum_{i'' \neq i,i',j \in (i_j \cap i'_j)} (X_{i,i'',j} + X_{i',i'',j}) + M(1 - XX_{i,i',j}) \tag{2.18}$$

$$\forall i, i', j \in (i_j \cap i'_j)$$

The variables $Z_{i,i',j}$ determine the position difference among two products produced in the same packing line. When $Z_{i,i',j}$ is equal to 0, product *i* is produced exactly before the *i'*. Variable $Z_{i,i',j}$ are then calculated in equation (2.18). As a result, according to constraint (2.17) the immediate precedence binary variable $XX_{i,i',j}$ takes the value 1 only when variables $Z_{i,i',j}$ are equal to zero. The binary variable $XX_{i,i',j}$ takes the value 1 when product *i'* is produced exactly after product *i*. The difference among the immediate and the global sequence binary variables is illustrated in Figure 2.3.

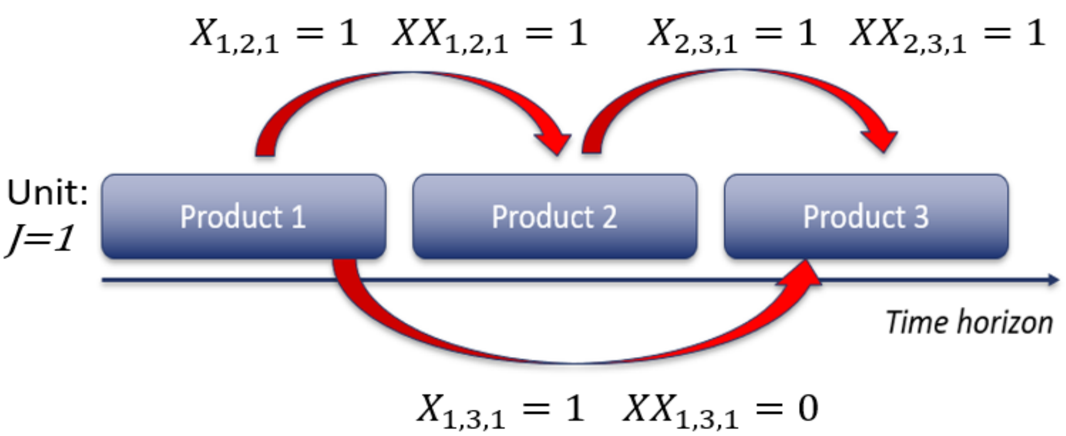

Figure 2.3 Immediate and general precedence binary variables

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Formulation/production stage constraint

$$\sum_{j}\sum_{i,i\in J_i}\sum_{\substack{i',\,i'\neq i,i'\in J_i\\ formula_i\neq formula_{i'}}}(XX_{i',i,j}) \leq Limit \tag{2.19}$$

Similarly to constraints (2.8), constraints (2.19) guarantee that the number of sequences between products with different recipes, $formula_i$, does not exceed an upper limit ($Limit$) which is determined by technical restrictions in the plant. To take into account the above, the usage of the immediate precedence binary variables is necessary.

Due date constraints

$$C_i \leq DDATE_i \tag{2.20}$$

Constraint (2.20) forces the completion time of a production order C_i to be lower or equal than a deadline, expressed by $DDATE_i$.

Time window constraints

$$C_i - T_i \geq Lower_i \quad \forall i, window_i = 1 \tag{2.21}$$

Similarly to the constraints (2.5), constraints (2.21) refers to products that have to be produced within a strict time slot.

Objective function

a) Minimization of makespan

$$\min C_{max} \geq C_i \qquad \forall i \tag{2.22}$$

b) Minimization of products changeover time

$$\min CT = \sum_{j}\sum_{i,i\in J_i}\sum_{\substack{i',\,i'\neq i,i'\in J_i\\ formula_i\neq formula_{i'}}} XX_{i,i',j}changeover_{i,i'} \tag{2.23}$$

`

While both objectives are often considered in scheduling problems, the continuous operation mode of the plant, determine the minimization of the total changeover time as the most appropriate one. Planned maintenance activities are considered as described in section 2.3.1.

2.4 Solution strategies

In general, the above MILP mathematical models, illustrate a strong advantage comparing with other models, due to their ability to provide the best solutions, especially for small or medium-sized problem instances. However, they cannot be used for the efficient solution of large-scale problem instances. Short solution times are a prerequisite for the acceptance of scheduling solutions by the industry.

Hence, MILP-based decomposition strategies are necessary, to satisfy the emerging industrial needs for practical implementation of scheduling solutions (Georgiadis et al., 2019a; Harjunkoski, 2016; Harjunkoski et al., 2014). It should be noted that the proposed models are suitable for the particular process structure which does not include recycle or complex recipes.

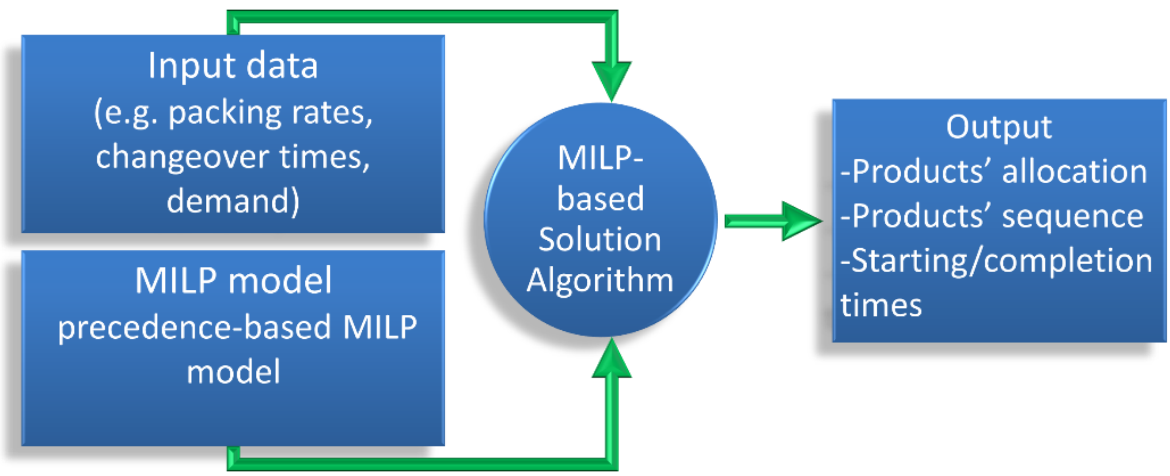

Figure 2.4 Schematic representation of the solutions strategies' structure

The MILP formulations, described in section 2.3, constitute the main core of the proposed solution strategies. They aim to generate good quality solutions, in short solution times, accepted by the plant. A brief schematic representation of the proposed solution strategies is illustrated in Figure 2.4.

2.4.1 Solution strategy – ST1

This strategy, consists of i) a unit-specific general precedence single-stage MILP model, described in subsection 2.3.2, ii) a constructive step and iii) an improvement step.

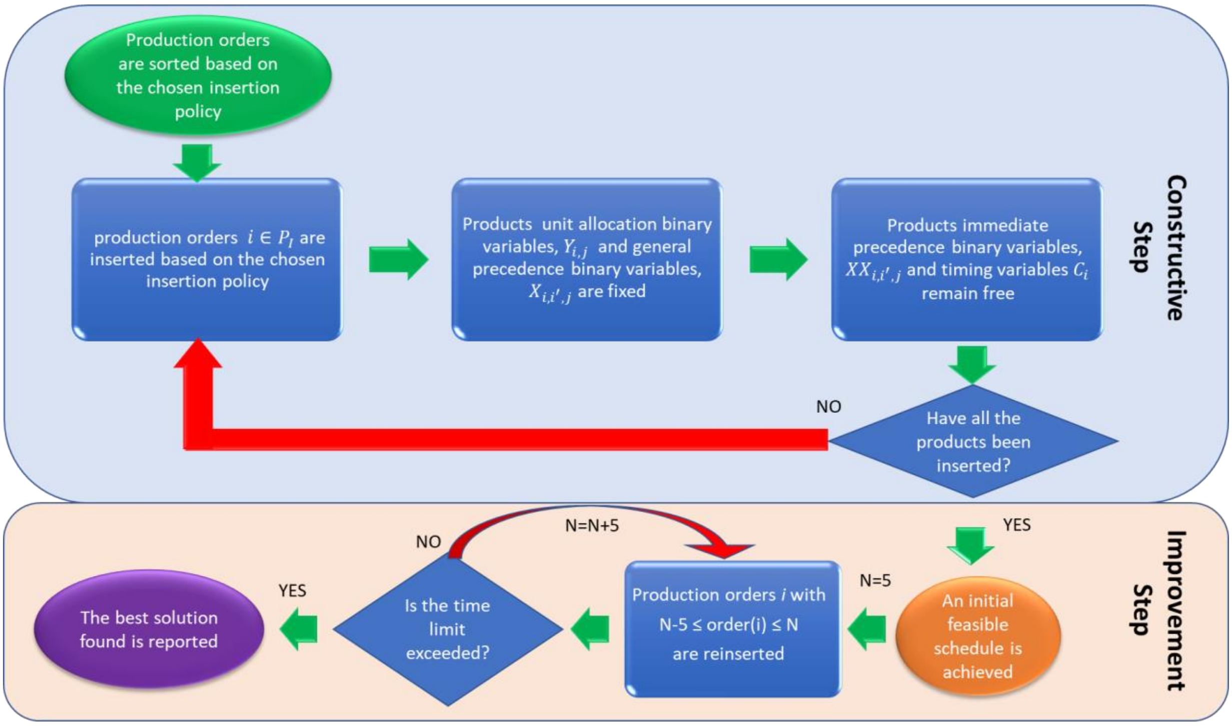

Figure 2.5 Schematic representation of the solution strategy – ST1

The key idea is to decompose the initial large-scale industrial scheduling problem into smaller tractable subproblems (Kopanos et al., 2010a). Firstly, an initial feasible solution is generated via the constructive step. The generated scheduled can be further improved via an integrated reordering step. Figure 2.5 illustrates the proposed decomposition technique.

2.4.1.1 Constructive step

At each iteration a subset of the product orders $i \epsilon P_I$ is scheduled. These MILP subproblems are solved much easier, as the complexity and the computational time is significantly decreased. After each iteration, the global sequencing variables $X_{i,i',j}$, as

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well as the allocation variables $Y_{i,j}$ of the inserted products are fixed. On the contrary, the timing variables C_i and the immediate precedence binary variables $XX_{i,i',j}$ remain free. The complete schedule is generated when finally, all products are inserted. An optimality gap of 0% is aimed at each iteration. However, industrial requirements impose an upper bound on the total computational time. Hence, a time limit of 3 minutes, has been set for the solution of each subproblem.

In order to provide better quality schedules, the last production orders, processed before the starting time of the new schedule, are set as the first production campaigns on each packing line. This way, the changeover time among the first product of the new schedule and the last produced campaign is also taken into account.

The simultaneous utilization of both general and immediate precedence binary variables, increases the flexibility of the algorithm, providing further alternatives during the insertion of new production orders. Figure 2.6 illustrates the allowed and the forbidden relative sequences of a new production order.

Furthermore, a set of efficient integer cuts are imposed in order to increase the computational efficiency. In particular, if a production order $i \epsilon P_I$ is allocated to a specific packing unit, then all precedence binary variables, related to other packing lines and later inserted products $i' \notin P_I$ are fixed to zero. These integer cuts decrease the complexity of the subproblems and improve the overall performance of the method. Constraints (2.24), (2.25), (2.26) and (2.27) express explicitly which binary variables are enforced to zero.

$$X_{i'i,,j} = 0 \qquad \forall i, i \epsilon P_I, Y_{i,j} = 0, i' \notin P_I, j \in (i_j \cap i'_j) \qquad (2.24)$$

$$X_{\iota,i',j} = 0 \qquad \forall i, i \epsilon P_I, Y_{i,j} = 0, i' \notin P_I, j \in (i_j \cap i'_j) \qquad (2.25)$$

$$XX_{i',i,j} = 0 \qquad \forall i, i \epsilon P_I, Y_{i,j} = 0, i' \notin P_I, j \in (i_j \cap i'_j) \qquad (2.26)$$

$$XX_{\iota,i',j} = 0 \qquad \forall i, i \epsilon P_I, Y_{i,j} = 0, i' \notin P_I, j \in (i_j \cap i'_j) \qquad (2.27)$$

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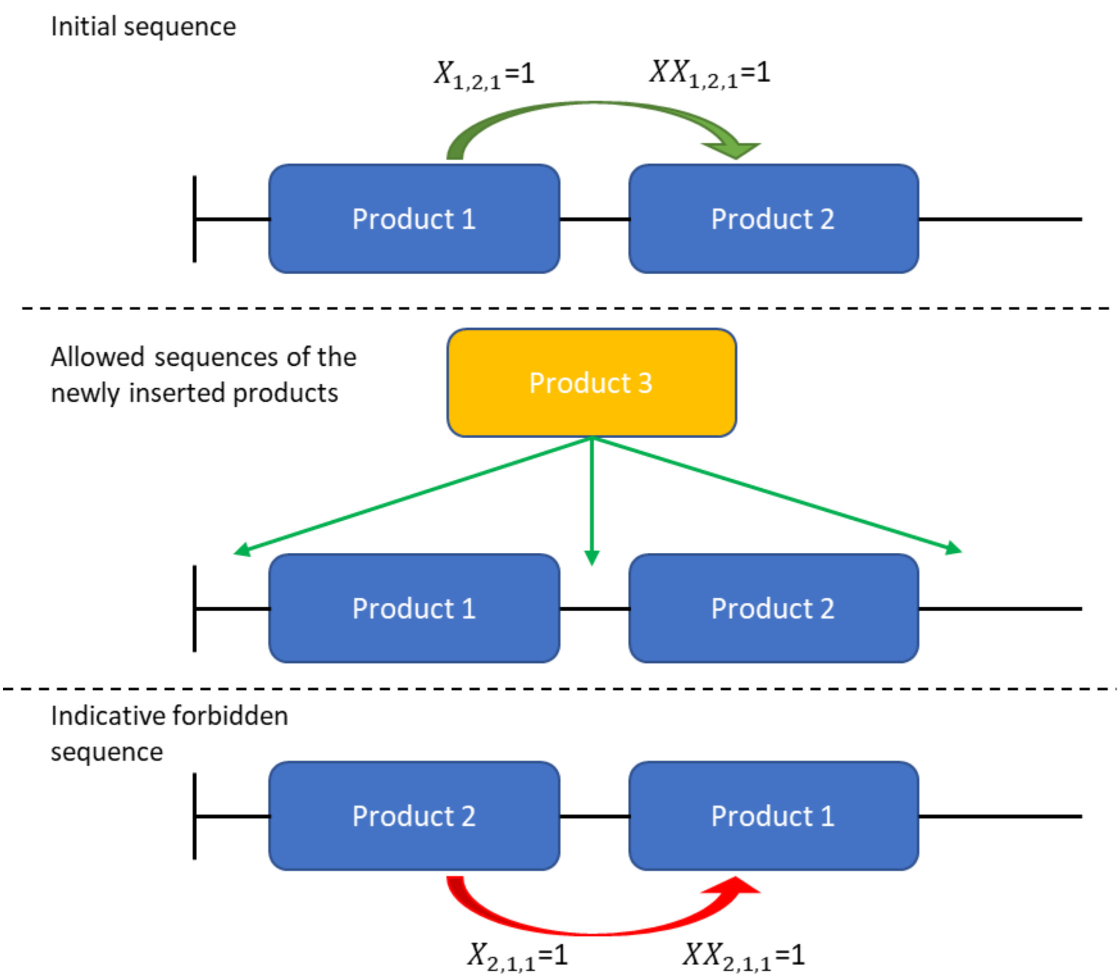

Figure 2.6 Allowed and forbidden sequences, according to the solution strategy ST1

The insertion policy constitutes a key step for both the computational efficiency and more importantly, for the quality of the solution. As a result, various insertion policies should be considered (Kopanos et al., 2010a). As the initial problem is solved iteratively, the number and sequencing of inserted products have to be decided. Two insertion criteria are used in order to avoid the generation of infeasible schedules. According to the first criterion, production orders are sorted firstly by the earliest due dates. Moreover, it is often observed that by minimizing the total changeover time, some packing lines are fully utilized. As a result, by inserting products with limited unit allocation flexibility in the last iterations, infeasible production schedules may be generated, due to the lack of unit availability. Thus, it is proposed to insert first products with limited unit allocation flexibility. In other words, products with limited allocation options to packing lines should be scheduled first. The planned maintenance activities are always scheduled first, by inserting a number of dummy product orders and fixing the allocation and ending time variable of them.

The number of inserted products $i \epsilon P_I$, has a huge impact in the initial feasible solution and the overall performance of the algorithm. As this number is increased, better quality solutions are expected due to larger degrees of freedom. However, more complex subproblems have to be solved and thus the computational time in increased. Taking into account current industrial requirements regarding the solution time and specific problem features, different insertion policies could be employed. Several real tests have illustrated, that a 5-by-5 product insertion policy is the optimal one for the problem under consideration since by inserting larger groups of products, the solution is not improved and the computational cost is increased, as it is discussed in section 2.5.2. In particular, an indicative comparison between 3 different insertion policies is presented in Table 2.8, depicting the advantages of a 5-by-5 insertion policy.

2.4.1.2 Improvement step – Reinsertion stage

The initial feasible solution, generated by the constructive step can be further improved via an iterative process. Following the main idea of previous research contributions (Basán et al., 2019; Kopanos et al., 2010a), a subset of products $i \in I^{rein}$ are released from the initial schedule, in order to achieve better unit allocation and sequencing decisions. The allocation, sequence and timing variables of products $i \in I^{rein}$ are relaxed. However, the allocation and the relative sequence variables of products $i \notin I^{rein}$ remain fixed. The products are reinserted iteratively and small subproblems are solved. Similarly to the constructive stage, a tradeoff between the computational time and the solution quality exists. Since the number of reinserted orders is increased, more complex subproblems have to be solved (Basán et al., 2019; Kopanos et al., 2010a). Since the proposed solution strategy focuses on solving a large-scale industrial problem, high computational times should be avoided as required by the industry. Hence, in this approach 5 products are reinserted in each iteration. According to the selected insertion policy in the constructive step and the comparison of results presented in Table 2.8 this insertion policy is the optimal one. A different number of reinserted products can be defined by the scheduler, depending on the underlying scheduling problem features and the desired plant policy. To fully satisfy the industrial requirements and to avoid high computational times, a time limit of 1200s is set. As the total computational time reaches this limit, the reinsertion stage is terminated, and the best solution found is reported. The improvement stage could also be terminated once a better solution is achieved, in case the number of production orders is too high.

2.4.2 Solution strategy – ST2

The main core of this strategy is the immediate-precedence model, described in subsection 2.3.1. Following a similar structure with solution strategy ST1, the proposed approach consists of i) the MILP model, ii) a constructive step and iii) an improvement step. A schematic representation of the proposed solution strategy is described in Figure 2.7.

2.4.2.1 Constructive step

A number of smaller-size subproblems is solved iteratively. On the contrary with the previously described decomposition technique, higher number of orders $i \in P_I$ are inserted in each iteration. The product's allocation binary variables, $Y_{i,j}$, as well as, the immediate precedence binary variables, $XX_{i,i',j}$, are fixed after the solution of each subproblem. In particular, a number of smaller sub-schedules, forms the constituent parts of the final schedule, that achieved when all production orders are inserted.

Contrary to the solution strategy ST1, even a larger number of products can be inserted at each iteration. Furthermore, global optimal solutions or solutions with an optimality gap of less than 3% are achieved in each subproblem. A limit on the solution time is again imposed, to avoid the generation of schedules which are not acceptable by the plant operators.

The size of each subproblem has a crucial impact on the quality of the final solution. Taking into account relevant industrial requirements it is of the highest importance to guarantee that all subproblems are solved with a small (0% -3%) optimality gap and within the time limit of 300 CPU s. The solution of smaller size subproblems tend to minimize the complexity, requiring less computational effort. However, at the same time, as all binary variables are fixed after the solution of each iteration, low quality final schedules are generated. On the other hand, a lower degree of decomposition may result to intractable subproblems, which cannot be solved to optimality in reasonable computational times. Hence, medium size subproblems should be preferred, which can be solved fast enough without sacrificing the quality of the solution. According to this tradeoff, several tests indicate that at maximum 35 products should be scheduled in each iteration. As it is demonstrated in Table 2.1, problem instances with even up to 35 products can be optimally solved by using the immediate precedence MILP model, since solutions with small optimality gaps (less than 3%) can be achieved within the 300 CPU s. On the contrary, in larger subproblems the intended optimality gaps cannot be guaranteed due to the large model sizes.

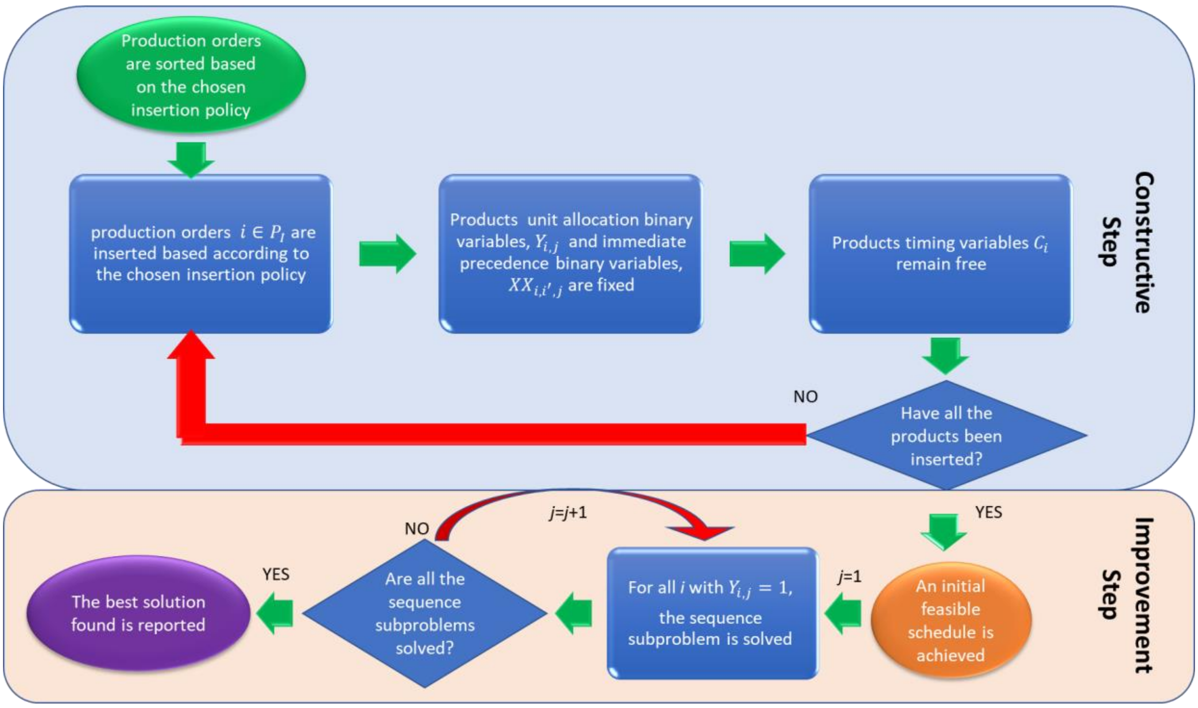

Figure 2.7 Schematic representation of the solution strategy - ST2

The insertion policy has also a huge impact in the performance of the decomposition algorithm. In the same concept with the previously described solution strategy ST1, products with the earliest due dates are inserted first. As a second criterion, products with limited unit allocation flexibility are inserted first. Possible maintenance activities are also scheduled before other production orders, by fixing the corresponding allocation variables and completion times. The immediate precedence-binary variables of the maintenance activities remain free.

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The last production campaigns, produced before the time horizon of interest, are also considered into the final solutions, by taking into account the corresponding changeover times. In particular, dummy production orders, with zero production time, T_i and the same features with the last production campaigns of the previous schedule, constitute the first production orders of each packing line. Hence, possible time-consuming changeover times, related to the first product sequence of each packing line, tend to be avoided, as they are also taken into account.

Effective integer cuts are imposed after the solution of each subproblem. Unnecessary sequencing combinations are eliminated, to reduce the computational effort. According to the constraints (2.28) and (2.29), if a production order, $i \epsilon P_I$, is not processed in a specific packing line $j \epsilon J_I$, ($Y_{i,j} = 0$), then all the related immediate precedence variables $XX_{i',i,j}$ and $XX_{\iota,i',j}$, for production orders $i' \notin P_I$ are forced to zero.

$$XX_{i',i,j} = 0 \qquad \forall i, i \,\epsilon\, P_I, Y_{i,j} = 0\,, i' \notin P_I, j \in \left(i_j \cap i'_j\right) \tag{2.28}$$

$$XX_{\iota,i',j} = 0 \qquad \forall i, i \,\epsilon\, P_I, Y_{i,j} = 0\,, i' \notin P_I, j \in \left(i_j \cap i'_j\right) \tag{2.29}$$

2.4.2.2 Improvement step – Reinsertion stage

An additional step is integrated into the solution algorithm to improve the initial generated schedule by the construction step. Given the allocation decisions, sequencing decisions of each product can be fully redefined to further reduce the sequence-dependent changeovers and the corresponding changeover times. Hence, the allocation variables of the products $Y_{i,j}$ are fixed. Sequencing subproblems, equal to the total number of packing units, are solved iteratively. A subset of products $i \in I^{reord}$, which have been assigned to the same production unit in the constructive stage, is allowed to be reordered by relaxing the related sequencing variables $XX_{i,i',j}$. Since only the sequencing variables are redefined, small subproblems are solved aced in each iteration with a 0% optimality gap achieved in less than 30 CPU s. After considering all possible sequencing problems of each packing unit, the final schedule is generated. A schematic representation of the proposed improvement step is also presented in Figure 2.7.

2.5 Industrial case studies

In order to assess the applicability and the efficiency of the proposed MILP models and solution strategies, a number of indicative real-life case studies of a consumer goods industry is considered. All models were implemented in GAMS (General Algebraic Modeling System), and solved utilizing the IBM ILOG CPLEX 12.0 solver on an 3.60 GHz Intel Core i7 7700 processor and 16 GB RAM.

In collaboration with the plant engineers, an efficient tool has been developed, to facilitate data exchange through a direct communication of GAMS and the ERP systems of the plant. A middle Microsoft Excel file is generated automatically, which includes customers demand, products special features, due dates and other essential information. The GAMS files are also called automatically and the problem under consideration is solved by utilizing an MILP model or a solution strategy. The generated solutions can be illustrated via interactive Gantt charts, or via Microsoft Excel sheets. Frequent late order arrivals, force the plant operators to modify the initial schedules in order to fully satisfy the demand. Due to the current industrial needs, the optimized schedules have to be generated in less than 20 minutes (1200s).

Several real-life case studies have been studied, and schedules have been generated by first solving the monolithic MILP models directly (described in subsection 2.3.1), or by implementing the proposed solution strategies ST1 and ST2. All problem instances are real industrial cases based on historical data and product demands. All results have been fully validated by the industry, and detailed comparisons, with manually generated schedules or with simulation tools have been made by the operators. Data related to the specific product features and the capacity of the plant cannot be disclosed due to confidentiality issues. Since, the plant operates continuously 24 hours per day the main objective is the minimization of the total changeover time. The changeover time savings can also lead to productivity improvements by reducing idle times of the production units.

2.5.1 Small and medium size problem instances

For small problem instances, the direct solution of the immediate precedence, single stage MILP model, described in subsection 2.3.1 is considered. Several tests illustrated that the immediate precedence MILP model provides better quality solutions comparing with the unit-specific general precedence (USGP) MILP model. A detailed comparison of the two proposed MILP models, for 3 indicative problem instances, is presented in Table 2.1. In particular, detailed information related to the computational features and solutions found within the time limit of 1200s CPU time is provided. It is observed that for the same problem instances the number of variables is strongly augmented by utilizing the USGP MILP model. As a result, the immediate precedence MILP model leads to better quality solutions and smaller optimality gaps. It is worth mentioning that for the third problem instance not even a feasible solution is reported by utilizing the USGP model.

Table 2.1 Comparison between the immediate precedence and the unit specific immediate precedence MILP models

Problem Instance	**1**		**2**		**3**	
Number of Products	35		45		55	
MILP Model	IPM	USGP	IPM	USGP	IPM	USGP
Constraints	3282	17866	5622	29776	7092	35436
Binary Variables	1520	3071	2660	5371	3380	6515
Continuous Variables	2458	10851	4058	18001	5008	21365
CPU time (s)	560	1200	1200	1200	1200	1200
Optimality gap (%)	0	3.8	5.6	22.6	8.9	-
Solution - Total changeover time (hours)	7.5	7.79	8.65	10.08	9.38	-

**IPM= Immediate precedence MILP model*
***USGP = Unit specific general precedence MILP model*

The majority of the products are described by high unit allocation flexibility, as most of the products packed in more than one packing lines. The generated schedules have been compared with the implemented schedules of the plant and results are summarized in Table 2.2. An exhaustive list of the computational features and the model sizes of the problems under consideration is presented in Table 2.3. As it is observed, significant changeover savings are achieved, thus resulting in a noticeably decrease in the total production time. In particular, the total changeover time is decreased by 33 minutes (6.72%), in the first case study and goes up to 222 minutes (22,05%) in the seventh one. These savings can also be translated to important improvements on the plant's production time, from 0.36% in the first case up to 2.30% in the last one. It should be also noted that, the total changeover time is decreased in all the MILP-based schedules compared to the schedules realized by the plant operators using simulation tools. In addition, higher improvements are observed in larger problem instances.

It is observed that small optimality gaps are achieved in all cases. Furthermore, in small problem instances global optimal solutions can be achieved within the imposed time limit. In Figure 2.8, an indicative Gantt chart is depicted including also a planned maintenance activity.

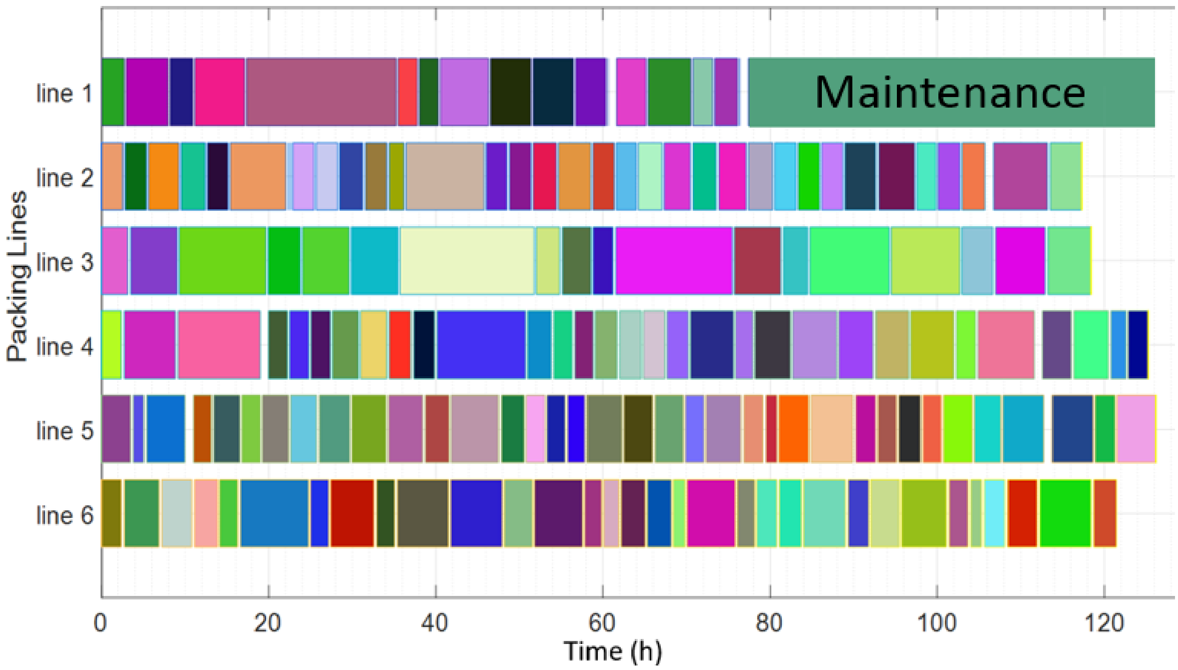

Figure 2.8 Indicative Gantt chart including maintenance activities

Two additional industrial case studies, with limited product-allocation flexibility to packing units, have been considered. The majority of products can be packed in one packing line only. Results are illustrated in the Table 2.4. A significant changeover time reduction is achieved in both cases, comparing with the operating policy of the plant. The changeover time savings lead to an improvement on the total production time of over than 0.5%. It has to be mentioned that 0% optimality gaps have been achieved in all the problem instances under consideration. A detailed list of the computational features and the model sizes of the problems under consideration is presented in Table 2.5.

Table 2.2 Comparison between the immediate precedence MILP model and the plant's schedules

Case study	Products to be scheduled	Changeover time reduction (minutes)	% Changeover time reduction	% Improvement on the total production time	CPU time (s)	Optimallity gap (%)
1	45	33	6,72%	0,36%	461	0
2	51	68	8,79%	0,61%	1200	3.2
3	49	75	9.34%	0.69%	1200	1.3
4	65	189	14,08%	2.32%	1200	6.1
5	68	201	20,99%	1,47%	1200	9.7
6	38	124	20.74%	2.16%	480	0
7	55	222	22.05%	2.30%	1200	5.7

Table 2.3 Computational features of the problem instances under consideration

Case study	Products to be scheduled	Constraints	Binary variables	Continuous variables
1	45	8198	3059	6077
2	51	10628	3,983	7,805
3	49	9778	3659	7205
4	65	17194	6447	12677
5	68	19040	7169	13876
6	38	5818	2163	4334
7	55	12448	4679	9077

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Table 2.4 Comparison between the proposed MILP model and the plant's schedules

Case study	Products to be scheduled	Changeover time reduction (minutes)	% Changeover time reduction	% improvement on the total production time	CPU time (s)	Optimallity gap (%)
1	41	78	11.04%	0.53%	536	0
2	33	69	11.86%	0.72%	351	0

Table 2.5 Computational features of the problem instances under consideration

Case study	Products to be scheduled	Constraints	Binary variables	Continuous variables
1	41	2891	1117	4992
2	33	2110	600	2682

In all cases, solution times are less than 20 CPU minutes and fully acceptable by the plant. Strict packing line allocation constraints can affect the efficiency of the model. The proposed modeling strategy is able to optimally solve real problems with approximately up to 65 products in 3 parallel lines. For larger problem instances, the computational cost is prohibitively high and as a result, not even a feasible solution can be generated within the imposed time limitation.

2.5.2 Large industrial problem instances

Several larger industrial problem instances have been also studied. A detailed comparison of the immediate precedence MILP model and the solution strategy ST1 is presented in Table 2.6. The initial feasible solutions are also presented in order to depict the benefits of the proposed improvement step. The decomposition algorithm results to significant savings in the changeover time by sacrificing part of the quality of the solution. More specifically, the changeover time is reduced by 57 minutes (5.37%) in the first case and by 67 minutes (5.83%) in the second one. These savings are translated into an improvement in the total production time, by 0.49% and 0.47% respectively.

Table 2.6 Comparison between the proposed MILP model, the solution strategy ST1 and the plant's schedules

Case study	Products to be scheduled	Approach	CPU time (s)	Changeover time reduction (minutes)	% Changeover time reduction	% Improvement on the production time
1	50	1st stage solution	405	47	4.43%	0.41%
		Improvement step	795	57	5.37%	0.49%
		IPM	1200	60	5.75%	0.54%
2	62	1st stage solution	670	52	4.53%	0.37%
		Improvement step	530	67	5.83%	0.47%
		IPM	1200	104	9.12%	0.75%
3	73	1st stage solution	728	356	24.39%	2.22%
		Improvement step	472	378	25.89%	2.35%
		IPM	1200	-	-	-

Although global optimal solutions cannot be achieved, relatively good quality schedules are generated in comparison with schedules obtained via the direct solution of the MILP monolithic model. In the first problem instance a 3.4% optimality gap has been achieved by utilizing the immediate precedence MILP model, while a solution with a 5.8% optimality gap has been obtained in the second one. Nevertheless, the proposed monolithic MILP model, can only be used for medium problem instances (case study 1 and case study 2), since in larger problems, such as case study 3, which involves 73 products, a feasible solution was not even obtained. In the third case study under consideration, a significant improvement in the changeover time is observed by applying solution strategy ST1. The total changeover time is reduced by 378 minutes (25.89%), which corresponds to an improvement of 2.35% in the total production time. The computational features of the case studies under consideration are presented in Table 2.7.

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Table 2.7 Computational features of the problem instances under consideration

Case study	Products to be scheduled	Constraints	Binary variables	Continuous variables
1	50	36771	6629	22251
2	62	55887	9625	34287
3	73	81396	17203	47597

The evaluation of the various insertion policies, is illustrated via an indicative comparison, presented in Table 2.8. This case study includes 50 products and 3 packing lines and it is solved using both the construction stage of the decomposition algorithm (ST1) and the monolithic MILP model, described in the subsection 2.3.1. The 5-by-5 insertion policy solution seems to be the optimal one. In addition, the computation time is significantly decreased by applying a 1-by-1, or 5-by-5 insertion policy. On the contrary, the application of a 10-by-10 insertion policy, increases the complexity of the subproblems and an optimality gap of 0% was not achieved under the solution time limitations. As a consequence, the computational time is gradually increased, and higher changeover time values are obtained.

Table 2.8 Comparison between the MILP model and solution strategy ST1 for different insertion policies

	IPM	Solution strategy (ST1)		
		Insertion policy 1-by-1	Insertion policy 5-by-5	Insertion policy 10-by-10
Changeover (hrs)	17.9	19.89	18.06	18.9
Computational Time (s)	3360	360	768	2172
Optimality gap (%)	0	-	-	-

**IPM= Immediate precedence MILP model*

Further representative large-scale, real-life case studies have also been considered and solutions were generated by utilizing solution strategy ST2. These case studies include more than 60 products, with high product allocation flexibility, and 3 packing lines. The insertion policy involves 35 products in each iteration. An extensive comparison between solutions obtained by the decomposition algorithm and real schedules realized

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by a plant is shown in Table 2.9. The computational time for the constructive step (1st stage) as well as the total computation time are also included to the same table. A significant changeover time reduction is achieved, from 90 minutes (9.01%), in the third problem instance, up to 925 (31.20%) minutes in the fifth one. These savings lead to an important improvement in the plant productivity. In particular, the total production time is decreased from 0.54% in the third case, up to 3.67% in the fifth one. It is worth mentioning that the initial feasible solutions can be significantly improved via the proposed improvement step. Indicatively, in the fifth problem instance, the total changeover time is decreased by 180 minutes (3 hours). Hence, the plant productivity is further improved by even 0.57%.

Table 2.9 Comparison between the proposed solution strategy ST2 and the plant's schedules

Case study	**Products to be scheduled**		**CPU time (s)**	**Changeover time reduction (minutes)**	**% Changeover time reduction**	**% Improvement on the production time**
1	74	1st stage solution	781	106	7.96%	0.73%
		Improvement step	148	180	13.51%	1.19%
2	66	1st stage solution	764	258	23.16%	2.43%
		Improvement step	192	301	27.02%	2.56%
3	63	1st stage solution	722	49	4.90%	0.31%
		Improvement step	106	90	9.01%	0.54%
4	66	1st stage solution	792	251	22.53%	2.36%
		Improvement step	212	317	28.47%	2.70%
5	119	1st stage solution	880	745	25.14%	3.10%
		Improvement step	314	925	31.20%	3.67%

The computational features of the case studies under consideration are presented in Table 2.10. In particular, the total number of equations and the large number of binary and continuous variables depicts the necessity to utilize decomposition algorithms in order to provide good quality solutions for larger problem instances. Indicatively, the fifth case study under consideration consists of even 42538 binaries and 29048 continuous variables

Table 2.10 Computational features of the problem instances under consideration

Case study	Products to be scheduled	Equations	Binary variables	Continuous variables
1	74	19480	6960	16421
2	66	17690	6629	13070
3	63	12928	4443	11895
4	66	17386	6588	12994
5	119	72386	42538	29048

2.5.3 Comparisons between the solution approaches

An extensive comparison between the two proposed solution strategies (ST1 and ST2) and the immediate precedence MILP model is presented. Three indicative medium-size case studies are considered, and an explicit comparison of the three methods is summarized in Table 2.11. As expected, the direct solution of the MILP model leads to good quality solutions with acceptable optimality gaps and within the time limit of 1200s. Furthermore, solution strategy ST2 provides better solutions than the ST1, with smaller computational times and therefore schedules are better than the ones implemented in the plant by the operators.

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Table 2.11 Comparison between the proposed MILP model, solution strategies ST1 and ST2 and the plant schedules

Case study		IPM*	ST1	ST2	Planners schedule
1	Number of products			49	
	Changeover time (hours)	13,39	15.8	15,32	16,8
	Total CPU time (s)	1200	1200	730	-
	Optimality gap	12%	-	-	-
2	Number of products			55	
	Changeover time (hours)	12.17	12.6	12.59	12.71
	Total CPU time (s)	1200	820	601	-
	Optimality gap	8%	-	-	-
3	Number of products			62	
	Changeover time (hours)	12.55	13.31	13.18	15.29
	Total CPU time (s)	1200	1200	820	-
	Optimality gap	9.3%	-	-	-

**IPM= Immediate precedence MILP model*

A further comparison between the two proposed solution strategies for larger-scale problem instances is illustrated in Table 2.12. Although, both techniques are able to decrease the total changeover time, strategy ST2 leads to higher reduction in the total changeover time with less computational effort. In addition, smaller optimality gaps are achieved in the solution of subproblems using strategy ST2, thus affecting the quality of the final solution. It is worth mentioning that no solution is reported from the MILP model within the time limit of 1200s.

The generated schedules, related to the third case study of the Table 2.11, are visualized via Gannt charts in Figure 2.9. In this problem instance, 62 products are scheduled within a time horizon of 90 hours. According to Table 2.11, the total changeover time is decreased by even 17.9% (2.7 hours) by utilizing the MILP model. A significant changeover time reduction is also achieved by using the solution strategies ST1 and ST2 (1.97 and 2.1 hours respectively).

Table 2.12 Comparison between solution strategies ST1 and ST2 and the plant schedules

Case study		ST1	ST2	IPM*	Planners schedule
1	Number of products		66		
	Changeover time (minutes)	871	855	-	1114
	Total CPU time (s)	839	886	1200	
2	Number of products		79		
	Changeover time (minutes)	932	863	1200	1115
	Total CPU time (s)	984	860	-	-

**IPM= Immediate precedence MILP model*

Given the huge production throughputs in the plant, the aforementioned savings correspond to a notable improvement of the overall profitability. The minimization of the total changeover time leads to an increased plant. The product dependent changeovers correspond to Cleaning-In-Place (CIP) and/or setup operations. Hence, the minimization of changeovers represents also savings in the utilization of plant resources, such as manpower, steam and energy consumption. Since the available production time is increased, maintenance activities could be planned more efficiently to avoid the unexpected units' breakdowns. As a result, the generated schedules lead to significant improvements in the overall plant efficiency something that has been also acknowledged by the underlying industry

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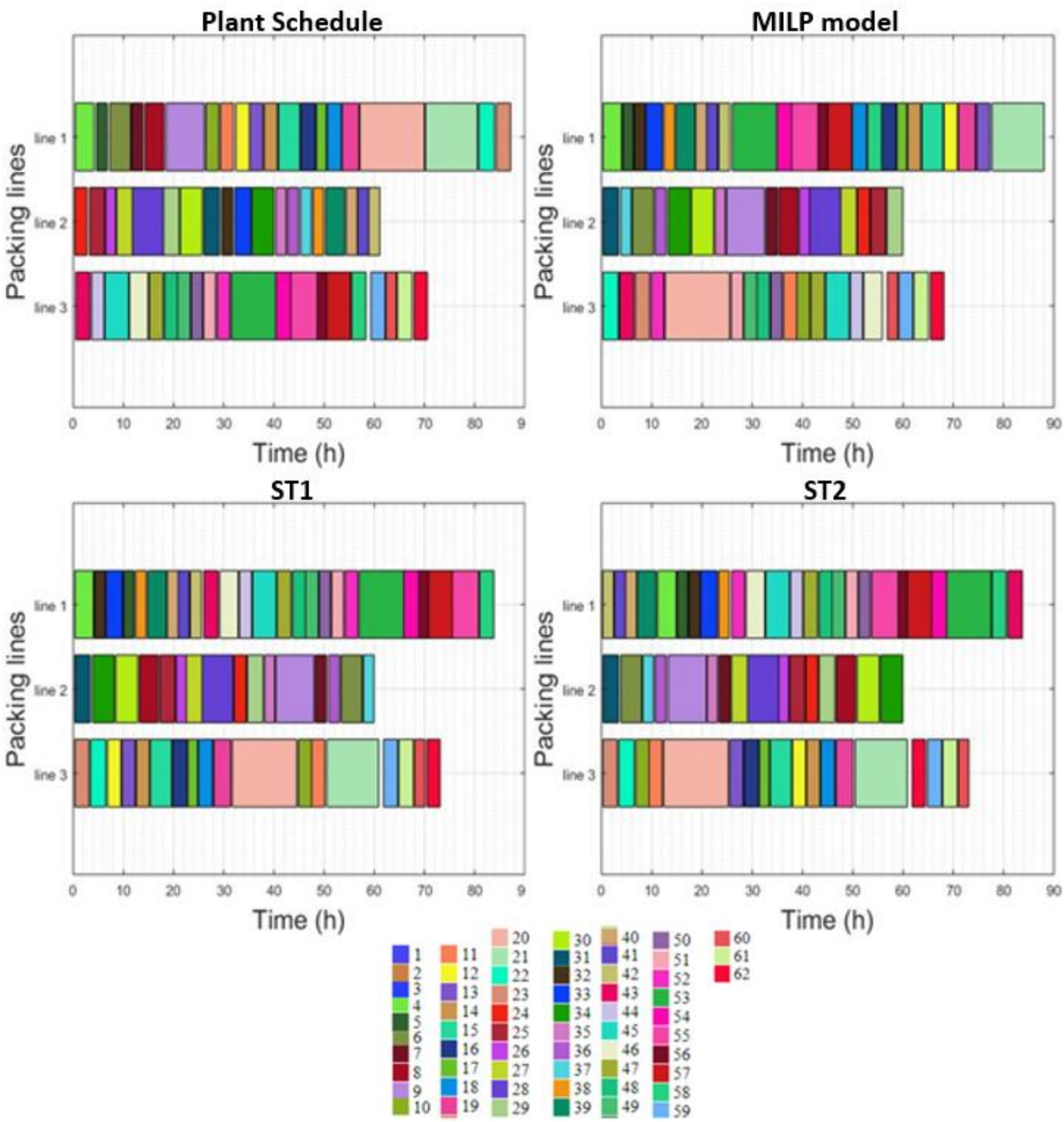

Figure 2.9 Gannt Charts for the plant schedule and optimized schedules

2.5.4 Real-time tests in the plant

For the purpose of fully validating the proposed methods, several real-time tests have been made in the plant. These tests are concerned with the arrival of new orders or order modification at real-time. As such, there is no comparison with existing scheduling approaches in the plant. Depending on the problem's complexity, different solution methods have been used. For smaller problem instances the direct solution of the immediate precedence MILP model is chosen, while the use of the ST2 method is preferred for larger instances. The generated optimized schedules fully satisfy all technical and operational constraints of the plant and they have been used to modify the manually generated schedule of the planners.

2.6 Conclusions

This work presents two MILP models and two solution strategies for the short-term scheduling of a real-life, large-scale, continuous process plant, of a multi-national consumer goods corporation. Emphasis is placed on the packing stage which constitute the main bottleneck of the plant. An extension of a previously proposed immediate precedence MILP model is used, for the efficient solution of medium size problem instances within solution time limitations imposed by the industry. The model takes into account all constraints relevant to the formulation stage in order to avoid infeasible schedules in the packing stage. Furthermore, two MILP-based decomposition strategies are developed for the solution of larger problem instances. Both techniques constitute problem-specific methods, resulting in relatively good quality solutions which compare favorably with schedules realized on the plant. Significant benefits related to the productivity of the plant are achieved, for a large set of realistic problems. All generated schedules have been fully validated by the industry. As expected for small or even medium size problems the direct solution of the immediate precedence MILP model is preferred. For larger problem instances solution strategy ST2 compares favorably with solution strategy ST1. The proposed approaches can provide significant support to scheduling decision makers in order to cope with challenging scheduling problems typically met in industrial facilities. This work illustrates the impact of scheduling optimization on the overall performance of an industrial facility and provides clear evidence for the need of using optimization-based techniques for challenging scheduling problems. Finally, this work highlights some serious obstacles that have to be confronted in order to successfully implement scheduling optimization methods in the industrial environment. The accuracy of the data is vital for the solution quality, hence the direct connection of the scheduling methods with the EPR system via integrated tools is critical. In the course of this study it was revealed that often the generated schedules should be easily modified by the plant operators, due to frequent unexpected events occurred, such as new order arrivals or order cancellations. For this end, the solution visualization via interactive Gannt charts provides the decision makers with flexibility and allows necessary adjustments prior to the final application of the proposed schedules.

Nomenclature

Indices/Sets

$i \in I$	Production orders
$j \in J$	Production units
I_J	Production orders that can be produced in unit *j*
P_I	Subset of production orders, inserted in the production schedule generated by a solution strategy

Parameters

Hor	The scheduling horizon under consideration
T_i	processing time of each product order $i \in I$
$changeover_{i,i'}$	Changeover time between two consecutive production orders $i \in I$ and $i' \in I$
$DDATE_i$	Due dates of product order $i \in I$
$Limit$	Upper limit of intermediate product's changeovers, coming from different formula types $formula_i$
$formula_i$	Formula type of intermediate product $i \in I$
D_i	Demand of product order $i \in I$
PR_i	Packing rate of product order $i \in I$
$window_i$	Parameter, taking the value 1, if a product campaign has to take place during a specific time window.
$Lower_i$	The lower limit of a production order's $i \in I$ starting time

Variables

$Y_{i,j}$	binary variable denoting that order $i \in I$ is allocated to unit *j*

C_i	completion time of order $i \in I$
$X_{i,i',j}$	global sequencing of product orders that is activated when order $i \in I$ is processed before order $i' \in I$
$XX_{i,i',j}$	immediate sequencing binary variable that is activated when order $i \in I$ is processed exactly before order $i' \in I$
C_{max}	total production makespan
CT	total changeover time
$Z_{i,i',j}$	Position difference of products $i \in I$ and $i' \in I$ which are both assigned to the same production unit j

3

Production scheduling of continuous make-and-pack processes with byproducts recycling

3.1 Introduction

Nowadays, several companies from various industrial sectors, such as food and beverages, pharmaceuticals, chemicals and fast-moving consumer goods (FMCGs), have adopted make-and-pack production processes. Due to variable production rates, a challenge typically met in continuous make-and-pack processes is the necessity to synchronize the production rates of consecutive stages (Elekidis and Georgiadis, 2021; Klanke et al., 2021). Thus, continuous stages are often decoupled by deploying intermediate storage vessels (Méndez and Cerdá, 2002).

Several early research contributions addressed the scheduling optimization problem of continuous make-and-pack processes, with intermediate storage facilities (Giannelos and Georgiadis, 2002; Méndez and Cerdá, 2002). However these approaches can only applied to small or medium sized problems Furthermore, later approaches are based on non-realistic assumptions and as a result they lead to infeasible or suboptimal solutions (Klanke et al., 2020, 2021; Yfantis et al., 2019). Hence, the development of efficient mathematical frameworks for the scheduling of large-scale continuous make-and-pack industries with flexible intermediate storage vessels constitutes a significant research gap.

Additionally, product-dependent changeovers, mainly occurred by cleaning operations, have to be minimized to increase the productivity of production facilities. In cases when cleaning with water can affect the quality of products, an undesirable amount of byproduct waste is generated between two consecutive campaigns. Usually, the byproducts can be recycled into the next production campaigns. This industrial policy is typically met in liquid detergents industries (Elekidis et al., 2019; Elekidis and Georgiadis, 2021). However, according to the best of our knowledge the modelling of byproducts recycling streams has not been addressed in consumer goods industries, while only a few research contributions have been focused on modelling the generation of byproduct waste in the paper industry (Castro et al., 2009c)

In this chapter, a new continuous-time, precedence-based MILP model is proposed for the scheduling optimization problem of multiproduct make-and-pack continuous processes, with intermediate storage facilities. The model includes allocation, timing and sequencing constraints. In the vast majority of scheduling models, a time horizon discretization approach is employed to efficiently handle material balance constraints (Klanke et al., 2021; Stefansson et al., 2011). This work introduces a new set of binary variables to accurately handle material balances and prevent overloading of storage vessels, without requiring any type of time horizon discretization. Furthermore, multiple production orders, produced by the same intermediate product type, are allowed to simultaneously be stored in the same storage vessel, via new explicit mass balance constraints. These constraints are based on extensions of previous precedence-based frameworks (Méndez and Cerdá 2002a). Additionally, in recently proposed MILP frameworks (Klanke et al., 2021, 2020; Yfantis et al., 2019), it is assumed that all types of intermediate products can be stored simultaneously in a single buffer tank, by considering only an aggregated capacity constraint. However, this assumption is not realistic, and it can lead to production schedules which cannot be implemented in practice. In the proposed MILP model explicit mass balance constraints are included for each buffer tank without relying on this assumption. Moreover, in the work of Klanke et al., (2021), it is assumed that all intermediate products are obligatorily stored into a buffer tank. This work relaxes this assumption by allowing, a more flexible storage and processing policy, since an intermediate product can either be temporarily stored into a buffer tank, or it can be routed directly to a packing line, bypassing the storage vessels. This flexible storage policy can lead to significant productivity benefits. Finally, new resource constraints related to the generation and recycling of byproduct waste are introduced to improve the utilization of raw materials and minimize byproducts management costs. A decomposition-based strategy is also proposed for the solution of real-life, large-scale industrial problem instances. Several case studies inspired by consumer goods industries have been solved, to illustrate the efficiency and applicability of the proposed framework using different objectives.

3.2 Problem statement

The process under consideration consists of two main continuous stages and it has been mainly inspired by multinational, large-scale, consumer goods industries (Elekidis et al., 2019). These industrial facilities operate as a make-and-pack production process. A plethora of raw materials is transformed into intermediate products through a continuous production/formulation process. The intermediate products are packaged in several package sizes or types and numerous final products are distributed to customers.

Depending on the specific product features, the bottleneck of the process could be either detected in the formulation or the packing stage. Since there is usually no clear production bottleneck, both stages have to be scheduled in detail. The utilization of intermediate buffers can provide the necessary flexibility to overcome these limitations and to synchronize both stages. The production time of each product can be modified, depending on the utilization of buffer tanks. An intermediate product can be temporarily stored in a buffer tank, or it can be directly transferred to packing lines bypassing storage. If an intermediate product is transferred to a buffer tank, both stages can operate at their highest throughput. Otherwise, the slowest stage determines the rate of both stages. Once a product campaign starts, it must be carried out until completion without interruption, as the splitting of product orders is not allowed.

Furthermore, frequent changes of raw materials, used in the formulation stage, lead to the generation and accumulation of undesirable amounts of byproduct waste. The generated liquid waste is recycled, so that small portions of it are reused into one of the next production campaigns without affecting the quality of products. This policy is typically met in liquid detergent production plants, as cleaning with water or air can cause the generation of undesirable amount of foam. Furthermore, if liquids are filed into tablets, even small amounts of water can dissolve the tablet film. A schematic representation of the plant layout is illustrated in Figure 3.1.

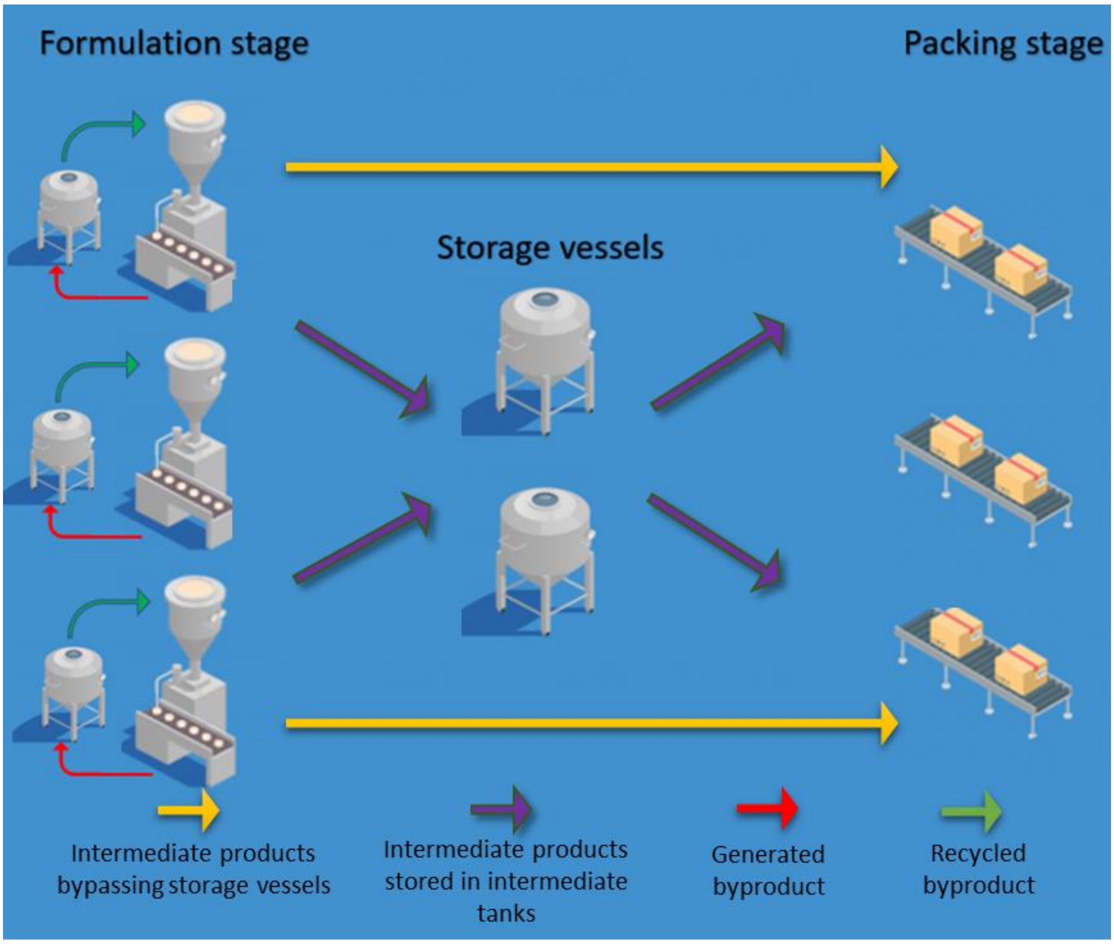

Figure 3.1 Plant layout

The problem under consideration can be formally stated as follows:

Given:

- A set of production orders $i, i' \in I$, produced by an intermediate product type (recipe), given by parameter f_i
- A set of processing units, $j \in J$
- A set of processing stages, $s \in S$
- A set of flexible intermediate storage tanks, $v \in V$, and their corresponding capacity, e_v

- Due dates of production orders, d_i
- Demand of product orders, dm_i
- Maximum production rates of production orders at each stage, $r_{i,s}$
- Changeover times, between the production of two consecutive production orders in each stage $n_{i,i',s}$
- Capacity of byproduct tanks of each processing unit of stage 1, cp_j.

Determine:

- The allocation of products to processing units, $Y_{i,j}$
- The allocation of products to intermediate storage tanks, $YV_{i,v}$
- The sequencing of product orders in the processing units, $X_{i',i,j}$
- The starting time, $ST_{i,s}$, the processing time, $T_{i,s}$, and the completion time, $CT_{i,s}$, of each production order at each stage.
- The produced, O_i, and the recycled, W_i , amount of byproduct
- The total production cost, TC

3.3 MILP model

In this section, an immediate-precedence, multi-stage model, of continuous processes is described. Instead of using a discrete-time horizon, a set of binary variables is introduced to correctly handle mass balance constraints. Product orders made of the same intermediate product may coexist in the same buffer tank for a period of time. An intermediate product can be temporarily stored in a storage vessel or it can be transferred directly to a packing line. However, a product campaign cannot be split.

Previous research works (Méndez and Cerdá 2002a; Giannelos and Georgiadis 2003), illustrated that several product campaigns are consecutively operated in the same unit, but at different processing rates. This policy is not typically met in real-life industrial facilities, since it leads to higher demand for manpower and generates unnecessary idle times (Méndez and Cerdá 2002a). In this work, if an intermediate product is transferred to a buffer tank, both stages operate at their highest speed. Otherwise, the slowest stage determines the rate of both stages. Constraints are grouped according to the type of decision (e.g., assignment, timing, sequencing, etc.) as follows. A detailed description of model sets, variables and parameters is presented in the nomenclature section at the end of the chapter.

Assignment constraints

$$\sum_{j\in (JI_i \cap JS_s)} Y_{i,j} = 1 \quad \forall i \in I, s \in S \tag{3.1}$$

Constraints (3.1) guarantee that each product order, i is assigned to one processing unit j, $(j \in JI_i)$, at each production stage s, $(j \in JS_s)$.

Product orders sequencing constraints

$$\sum_{i' \in I:\, i' \neq i} X_{i',i,j} \leq Y_{i,j} \quad \forall i \in I, j \in JI_i \tag{3.2}$$

$$\sum_{i' \in I:\, i' \neq i} X_{i,i',j} \leq Y_{i,j} \quad \forall i \in I, j \in JI_i \tag{3.3}$$

$$\sum_{i \in IJ_j} \sum_{i' \in IJ_j :\, i' \neq i} X_{i,i',j} + 1 = \sum_{i \in IJ_j} Y_{i,j} \quad \forall j \in J \tag{3.4}$$

Binary variables $X_{i',i,j}$ define the local immediate precedence between two products i and i'. They are equal to 1, only if a product order i' comes immediately after production order i in processing unit j. Constraints (3.2) and (3.3) ensure that, if production order i is allocated to packing line j, at most one production order comes before and after it, respectively. If a production order is processed first or last, then it has no predecessor or successor. According to constraints (3.4), the total number of sequences in a processing unit j has to be equal to the total number of produced orders minus one.

Timing constraints

$$CT_{i,s} = T_{i.s} + ST_{i,s} \quad \forall i \in I, s \in S \tag{3.5}$$

$$T_{i,s} = \sum_{v \in V} YV_{i,v}\, pm_{i,s} + pl_i \left(1 - \sum_{v \in V} YV_{i,v}\right) \quad \forall\, i \in I, s \in S \tag{3.6}$$

$$\sum_{v \in V} YV_{i,v} \le 1 \qquad \forall\, i \in I \tag{3.7}$$

According to constraints (3.6), if an intermediate product is transferred to a buffer tank, both stages operate at their highest speed and the processing time is equal to the minimum processing time. Otherwise, the slowest stage determines the rate of both stages and therefore the processing time is equal to the maximum pl_i. In addition, constraints (3.5) express that the completion time of each product is equal to the starting time plus the processing time. Constraints (3.7), guarantee that each product order is assigned at most in one storage vessel.

$$ST_{i',s} \ge CT_{i,s} + X_{i,i',j} n_{i,i',s} - h(1 - X_{i,i',j}) \tag{3.8}$$

$$\forall\, i \in I, i' \in I, s \in S, j \in (\, JS_s \cap (JI_i \cap JI_{i'})\,) : i' \ne i$$

$$ST_{i',s} \le CT_{i,s} + L_{i,i',s} + X_{i,i',j} n_{i,i',s} + h(1 - X_{i,i',j}) \tag{3.9}$$

$$\forall\, i \in I, i' \in I, s \in S, j \in (\, JS_s \cap (\, JI_i \cap JI_{i'})\,) : i' \ne i$$

The big-M constraints (3.8) define the timing decisions of each product order. Since a product order i' is operated immediately after product order i, in stage s, the starting time $ST_{i',s}$ has to be larger than the sum of the completion time $CT_{i,s}$ and the related changeover time $n_{i,i',s}$. On the other hand, if binary variable $X_{i,i',j}$, is equal to 0 and the specified sequence does not take place, the constraints are relaxed.

Extending previous precedence-based frameworks (Méndez and Cerdá 2002a; Elekidis, Corominas, and Georgiadis 2019; Cerdá, Cafaro, and Cafaro 2020), constraint (3.9) is also included in the model framework, to examine possibly generated idle times. Thus, the starting time of each product order $ST_{i',s}$ has to be larger than the sum of the ending time of the previously operated product $CT_{i,s}$, the related changeover time $n_{i,i',s}$ and the idle time between the consecutive campaigns, $L_{i,i',s}$.

Buffer timing constraints

Constraints (3.10) and (3.11) and establish the sequence of production orders, containing different intermediate products ($f_i \neq f_{i'}$), that are temporarily stored in the same intermediate buffer tank. If a production run i' is stored in a storage vessel v after a production run i , the starting time $ST_{i',1}$ has to be bigger than the completion time $CT_{i,2}$.

$$CT_{i,2} \leq ST_{i',1} + h(2 - YV_{i,v} - YV_{i',v}) \ + h(1 - XV_{i,i',v}) \qquad (3.10)$$

$\forall \ i \in I, i' \in I, v \in V : i' > i$

$$CT_{i',2} \leq ST_{i,1} + h(2 - YV_{i,v} - YV_{i',v}) \ + hXV_{i,i',v} \qquad (3.11)$$

$\forall \ i \in I, i' \in I, v \in V : i' > i$

Usually, production orders that are made by the same intermediate product may coexist in the same buffer tank for some period of time. Extending previous precedence-based frameworks (Méndez and Cerdá 2002a; Cerdá, Cafaro, and Cafaro 2020), constraints (3.12) and (3.13) are introduced to account for this case.

$$ST_{i',1} \leq ST_{i,1} + h(2 - YV_{i,v} - YV_{i',v}) \ + h(1 - XV_{i',i,v}) \qquad (3.12)$$

$\forall i \in I, i' \in I, v \in V : i' > i,\ f_i = f_{i'}$

$$ST_{i,1} \leq ST_{i',1} + h(2 - YV_{i,v} - YV_{i',v}) + hXV_{i',i,v} \quad (3.13)$$

$\forall i \in I, i' \in I, v \in V : i' > i,\ f_i = f_{i'}$

In particular, since the two product orders are made by the same recipe ($f_i = f_{i'}$), they can be simultaneously stored in the same tank. In that case, product i can be filled into the storage tank before the completion of packing stage of product i' and the starting time $ST_{i,1}$ has to be greater than the starting time $ST_{i'1}$, if they are sequentially stored in the same vessel ($XV_{i',i,v}$ =1).

Definition of auxiliary binary variables YO_i, $Z_{i,i'}$, $P_{i,i'}$ and $K_{i,i'}$

An auxiliary binary variably, YO_i, is introduced to satisfy the necessary mass balance constraints for each product order. Binary variables, YO_i, take the value 1, only if a product order starts packing, $ST_{i,2}$, later than completing the formulation stage ($CT_{i,1}$).

$$ST_{i,2} \geq ST_{i,1} - h(1 - YO_i) \quad \forall i \in I \quad (3.14)$$

$$ST_{i,2} \geq CT_{i,1} - h(1 - YO_i) \quad \forall i \in I \quad (3.15)$$

A new set of binary variables is furthermore introduced to efficiently satisfy storage capacity constraints, for products that may coexist in the same buffer tank. The binary variables $Z_{i,i'}$ take the value 1, only if a product order i starts packing ($ST_{i,2}$) earlier than the completion time of the formulation stage ($CT_{i',1}$) of product order i'.

$$ST_{i,2} \geq CT_{i',1} - hZ_{i,i'} \quad \forall i \in I, i' \in I : i' \neq i \quad (3.16)$$

$$ST_{i,2} \leq CT_{i',1} + h(1 - Z_{i,i'}) \quad \forall i \in I, i' \in I : i' \neq i \quad (3.17)$$

The binary variables $P_{i,i'}$ take the value 1, only if a product order i starts packing ($ST_{i,2}$) earlier than the starting time of the packing stage ($ST_{i',2}$) of product order i'.

`

$$ST_{i,2} \geq ST_{i',2} - hP_{i,i'} \quad \forall i \in I, i' \in I : f_i = f_{i'} \tag{3.18}$$

$$ST_{i,2} \leq ST_{i',2} + h(1 - P_{i,i'}) \quad \forall i \in I, i' \in I : f_i = f_{i'} \tag{3.19}$$

The binary variables $K_{i,i'}$ take the value 1, only if a product order i completes formulation ($CT_{i,1}$) earlier than the completion time of the formulation stage ($CT_{i',1}$) of product order i'.

$$CT_{i,1} \geq CT_{i',1} - hK_{i,i'} \quad \forall i \in I, i' \in I : f_i = f_{i'} \tag{3.20}$$

$$CT_{i,1} \leq CT_{i',1} + h(1 - K_{i,i'}) \quad \forall i \in I, i' \in I : f_i = f_{i'} \tag{3.21}$$

Mass balance constraints

Since all storage tanks have finite capacities, the net amount of material stored in a tank should never exceed its capacity. Assuming that the production rate of an intermediate is greater than the overall consumption rate (packing rate), the capacity constraints should only be enforced at the completion time of the formulation stage; see the yellow arrows in Figure 3.2. However, one cannot guarantee that the production rate in the formulation stage will be greater than or equal to the overall consumption rate for any product. Thus, the capacity constraints must also be enforced at the starting time of every packing order; see the red arrow in Figure 3.2, (Méndez and Cerdá 2002a).

Figure 3.2 illustrates the profile of the buffer level when multiple products belonging to the same product family (they are produced by the same intermediate product) can be stored simultaneously in the same tank. The production rate of product 1 is higher than its packing rate. Therefore, the capacity constraints have to be enforced at the completion time of its formulation stage (t1). On the contrary, the packing rate of product 2 is higher than the rate of its formulation stage and therefore capacity constraints must also be enforced at the starting time of the packing order of product 2 (t3).

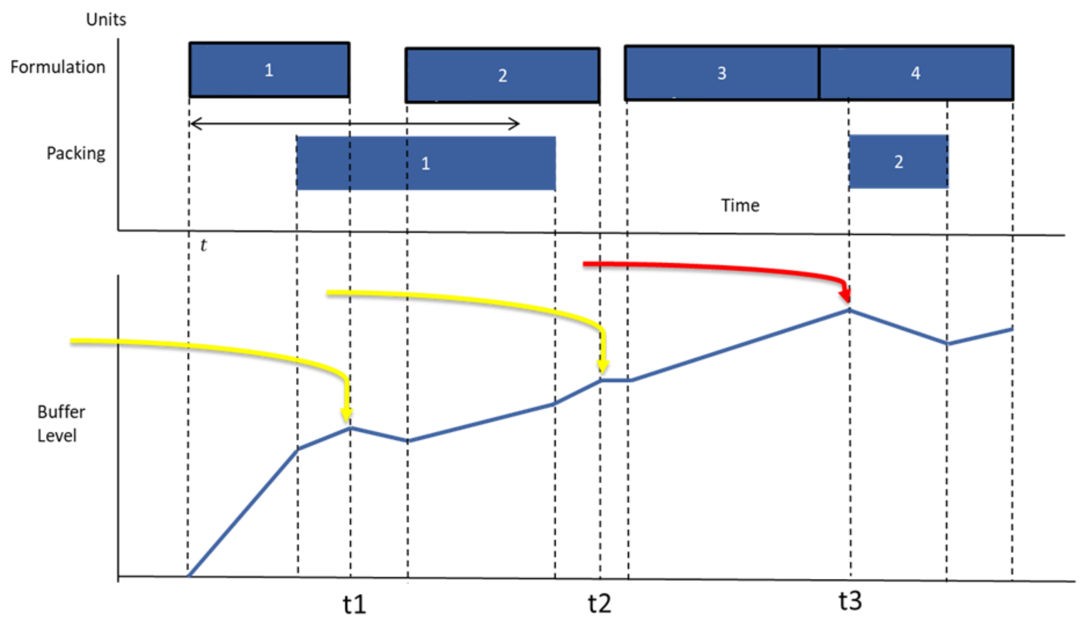

Figure 3.2 Buffer level where the coexistence of multiple product orders is allowed

The variable $Q_{i,}$ expresses the maximum stored amount of product order i, if product i does not coexist with other product orders in the same storage tank.

$$Q_i \leq \sum_{v \in V} e_v \, YV_{i,v} \quad \forall i \in I \tag{3.22}$$

Constraint (3.22) ensures that the stored amount of a product order ($Q_{i,}$), does not exceed the capacity of the storage vessel (e_v), only if this product is allocated to a storage vessel v.

Constraints, (3.23), (3.24) and (3.25) define the value of variable $Q_{i,}$. The auxiliary binary variable YO_i has a vital role in mass balance constraints. According to constraints (3.14) and (3.15), $YO_{i,}$ takes the value 1, only if a product order starts packing ($ST_{i,2}$) later than completing the formulation stage ($CT_{i,1}$). In this case, storage constraints are forced at the end of the formulation stage. In Figure 3.2, variable YO_1 is 0 while variable YO_2 is 1.

$$Q_i \geq pm_{i,1}\, r_{i,1} \sum_{v \in V} YV_{i,v} - pm_{i,1}\, r_{i,1}(1 - YO_i) \quad \forall i \in I \tag{3.23}$$

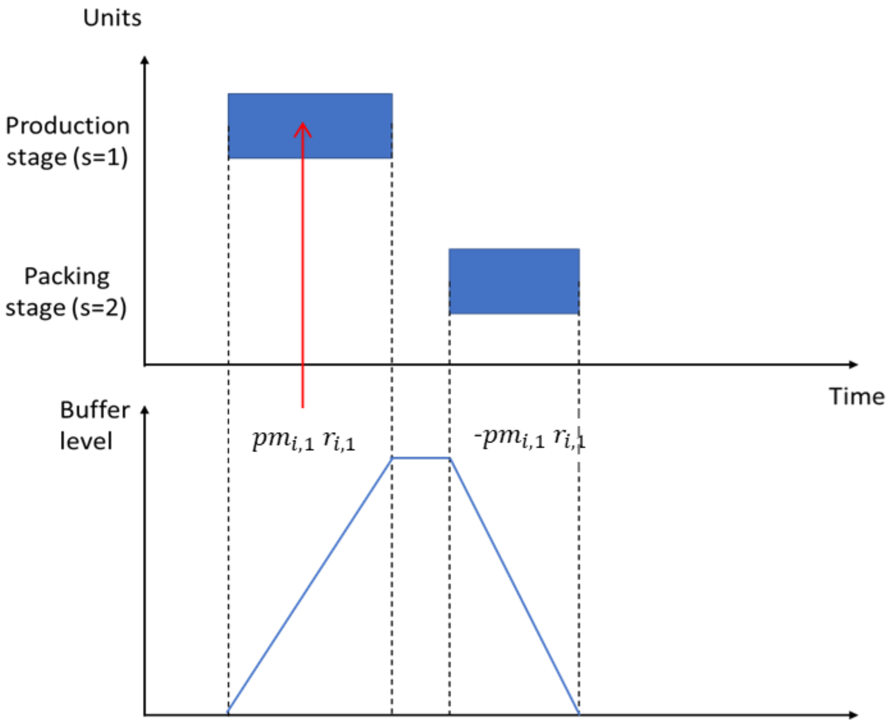

Figure 3.3 Illustrative example where the two stages do not operate simultaneously

Constraints (3.23) are activated when there is no overlapping between the two stages ($YO_{i,} = 1$). Under these circumstances, the stored amount Q_i should be equal to $pm_{i,1}r_{i,1}$, as it is depicted in Figure 3.3. Constraint (3.23) is activated only if product *i* is stored in one of the available buffers ($\sum_v YV_{i,v} = 1$) . If variable $YO_{i,} = 0$, the term $pm_{i,1}r_{i,1}$ is utilized as big-M value and the RHS value of the constraint is forced to zero.

On the other hand, if a packing operation starts while the related intermediate product is still filled into a buffer tank ($YO_{i,} = 1$), constraints (3.24) and (3.25) are activated. Two separate cases are examined. Constraints (3.24) define the stored amount $Q_{i,}$ in cases where the main bottleneck is detected in the first stage ($r_{i,2} > r_{i,1}$,$pm_{i,2} < pm_{i,1}$). Under these circumstances, the stored amount is equal to the term $(ST_{i,2} - ST_{i,1})r_{i,1}$. An illustrative example is presented in Figure 3.4.

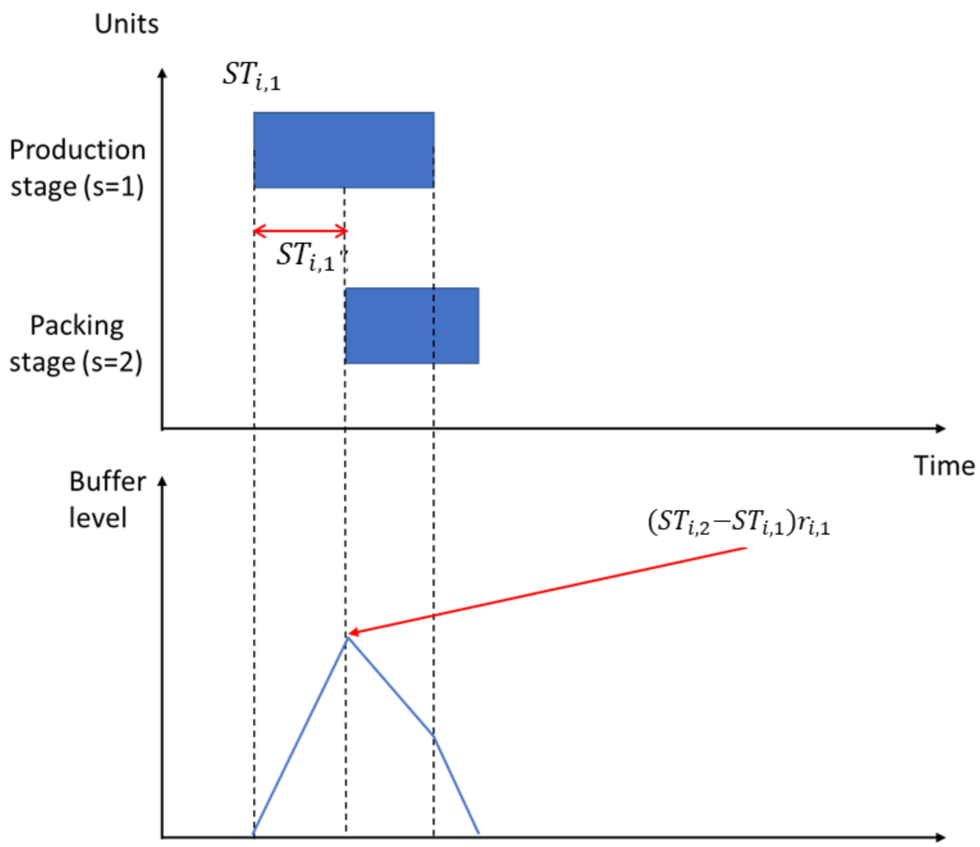

Figure 3.4 Indicative example where formulation stage constitutes the main bottleneck

Furthermore, the term $(d_i - pm_{i,2})\, r_{i,1}$ plays the role of big-M value, in constraints (3.24). The selection of the big-M values has a crucial impact on the computational complexity of a MILP model and the selected values should be as small as possible. Since variable $ST_{i,2}$ is less than or equal to the corresponding due date (d_i) minus its corresponding minimum processing time $pm_{i,2}$, ($ST_{i,2} \leq d_i - pm_{i,2}$) and variable $ST_{i,1}$ is greater than zero ($ST_{i,1} \geq 0$), the first term of the RHS is less than or equal to the term $(d_i - pm_{i,2})\, r_{i,1}$.

$$Q_i \geq (ST_{i,2} - ST_{i,1})r_{i,1} - (d_i - pm_{i,2})\, r_{i,1}\, YO_i - \qquad (3.24)$$

$$-(d_i - pm_{i,2})\, r_{i,1}(1 - \sum_{v \in V} YV_{i,v}) \quad \forall i \in I : pm_{i,2} < pm_{i,1}$$

$$Q_i \geq pm_{i,1} r_{i,1} \sum_{v \in V} YV_{i,v} - (CT_{i,1} - ST_{i,2}) r_{i,2} - \tag{3.25}$$

$$-[pm_{i,1} r_{i,1} + (d_i - pm_{i,2} - pm_{i,1})\, r_{i,2}] YO_i \qquad \forall i \in I : pm_{i,1} \leq pm_{i,2}$$

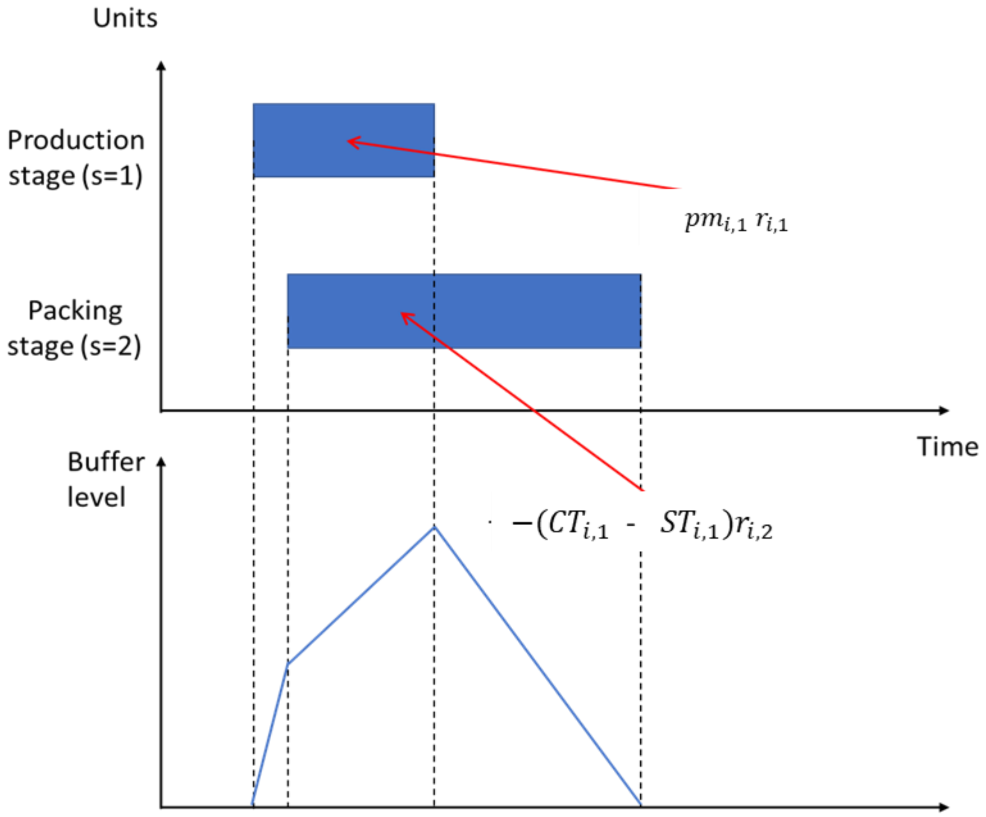

Figure 3.5 Illustrative example where the main bottleneck is detected in the packing stage

In cases like the one illustrated in Figure 3.5, where the main bottleneck is detected in the packing stage $(r_{i,1} \geq r_{i,2}, pm_{i,1} \leq pm_{i,2})$, the stored amount $Q_{i,}$ is defined by constraint (3.25). Then the stored amount is equal to the inserted product ($pm_{i,1} r_{i,1}$) minus the exported quantity which is equal to the term $(CT_{i,1} - ST_{i,2}) r_{i,2}$.

The term $[pm_{i,1} r_{i,1} + (d_i - pm_{i,2} - pm_{i,1})\, r_{i,2}]$ is used as a big-M value and is activated if variable YO_i=1. In particular, the term $pm_{i,1} r_{i,1}$ is included to cancel the term of the inserted amount while the term $(d_i - pm_{i,2} - pm_{i,1})\, r_{i,1}$ is used to cancel the term of the exported amount. If variable YO_i=1 then $(ST_{i,2} \geq CT_{i,1})$ and therefore the term $-(CT_{i,1} -$

$ST_{i,2})r_{i,2} \geq 0$. Since $ST_{i,2} \leq d_i - pm_{i,2}$ and $CT_{i,1} \geq pm_{i,1}$, it is concluded that $-(CT_{i,1} - ST_{i,2})r_{i,2} \leq (d_i - pm_{i,2} - pm_{i,1})\, r_{i,2}$.

Mass balance constraints for product orders produced by the same intermediate product type (recipe)

As has been previously mentioned, production orders which are made by the same intermediate product ($f_i = f_{i'}$), may be stored simultaneously in the same buffer tank for some period of time. To ensure that the net amount of storage material does not exceed the capacity of storage vessels, explicit mass balance constraints are enforced both at the completion time of formulation stage and at the starting time of packing stage of each product.

Mass balance constraints at the completion time of formulation stage

$$QT_i \geq \sum_{i' \in I:\ f_i = f_{i'}} QI_{i',i} - \sum_{i' \in I:\ f_i = f_{i'}} QE_{i',i} \quad \forall i \in I \tag{3.26}$$

$$QT_i \leq \sum_{v \in V} e_v YV_{i,v} \quad \forall i \in I \tag{3.27}$$

The variable QT_i is introduced to define the net amount stored, at the completion time of formulation stage of product i, ($CT_{i,1}$). According to constraints (3.26) the accumulated amount is greater than the total inserted amount, $QI_{i',i}$, minus the total exported quantity, $QE_{i',i}$. The orders i' are made by the same recipe ($f_i = f_{i'}$) and may coexist in the same buffer tank with product i. Constraints (3.27) guarantee that the stored amount ($QT_{i,}$), will not exceed the related capacity of vessel v, (e_v).

To satisfy capacity constraints (3.27), the mathematical model tends both to decrease the total inserted amount and increase the exported amount. Thus, a set of inequalities are additionally introduced to impose the required bounds on both variables $QI_{i',i}$ and $QE_{i',i}$. The corresponding inequality constraints are presented below.

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$$QE_{i',i} \leq dm_{i'} \sum_{v \in V} (XV_{i',i,v} + XV_{i,i',v}) \quad \forall i \in I, i' \in I : f_i = f_{i'} \tag{3.28}$$

$$QE_{i',i} \leq (CT_{i,1} - ST_{i',2}) r_{i',2} + d_i r_{i',2} (1 - Z_{i',i}) \quad \forall i \in I, i' \in I : f_i = f_{i'} \tag{3.29}$$

Variables $QI_{i',i}$ are defined by a set of big-M constraints (3.28) and (3.29). The auxiliary variable $K_{i',i}$, plays a significant role in mass balance constraints. More specifically, variable $K_{i,i'}$ takes the value 1, only if a product order i' completes its formulation ($CT_{i,1}$) earlier than the completion time of the formulation stage ($CT_{i',1}$) of product order i'.

Similar to constraints (3.24) the term $d_i r_{i',1}$ plays the role of a big-M value in constraints (3.29). Variable $CT_{i,1}$ is less than or equal to the corresponding due time, ($CT_{i,1} \leq d_i$), while variable $ST_{i',1}$is greater than o equal to zero ($ST_{i',1} \geq 0$). Therefore, the value of the term $(CT_{i,1} - ST_{i',1}) r_{i',1}$ is less than or equal to $d_i r_{i',1}$.

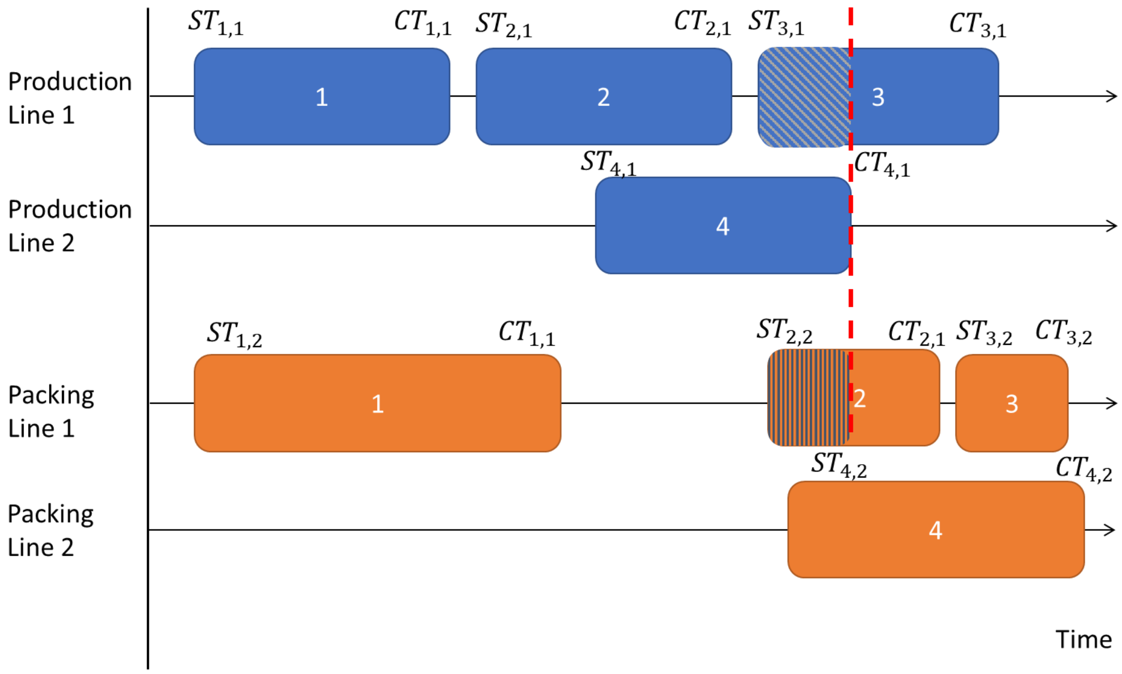

Figure 3.6 Illustration of the role of $QI_{i,i'}$ and $QE_{i,i'}$ variables

Once the variable $K_{i,i'}$ is equal to 1, the inserted amount should be equal to the total amount $dm_{i'}$, according to constraints (3.28). Otherwise, constraints (3.29) are activated and the inserted amount is forced to be equal to the term $(CT_{i,1} - ST_{i',1})r_{i',1}$. Both constraints (3.28) and (3.29) should be activated only if both products i and i' are stored at the same tank, ($\sum_v(XV_{i',i,v} + XV_{i,i',v}) = 1$). For the sake of the clarity of this idea, an illustrative example is shown in Figure 3.6.

$$QE_{i',i} \leq dm_{i'} \sum_{v \in V}(XV_{i',i,v} + XV_{i,i',v}) \quad \forall i \in I, i' \in I : f_i = f_{i'} \tag{3.30}$$

$$QE_{i',i} \leq (CT_{i,1} - ST_{i',2})r_{i',2} + d_i r_{i',2}(1 - Z_{i',i}) \qquad \forall i \in I, i' \in I : f_i = f_{i'} \tag{3.31}$$

$$QE_{i',i} \leq dm_{i'} Z_{i',i} \quad \forall i \in I, i' \in I : f_i = f_{i'} \tag{3.32}$$

To define variables $QE_{i',i}$, auxiliary variable $Z_{i',i}$, is utilized. Constraints (3.30) and (3.32) ensure that the amount of $QE_{i',i}$ does not exceed the total amount of product i', ($dm_{i'}$). If a product i' either starts packing ($ST_{i',2}$) later than the completion time of the formulation stage ($CT_{i,1}$) of product i, ($Z_{i',i} = 0$), or it is not allocated to the same buffer tank ($\sum_v(XV_{i',i,v} + XV_{i,i',v}) = 0$), variables $QE_{i',i}$ are forced to zero. In case that a packing operation has not been completed until the time point under consideration, the variable $QE_{i',i}$ is limited by the term $(CT_{i,1} - ST_{i',2})r_{i',2}$, as it is guaranteed by constraints (3.31). Similar to constraints (3.29) the term $d_i r_{i',2}$ is utilized as a big-M value in constraint (3.31).

To illustrate the role of variables $QI_{i,i'}$ and $QE_{i,i'}$ an indicative example is depicted in Figure 3.6. The mass balance constraints can be applied at the end of product 4 ($CT_{4,1}$). Since all the amount of product 1 has already been filled into the buffer tank at the time under consideration ($K_{1,4,} = 1$), the variable $QI_{1,4}$ should be equal to the total amount of product 1 (dm_1). The aforementioned approach is applicable in the case of product 2 as well. On the other hand, only the line-shaded part of product 3 has been filled into the tank at the time under consideration ($K_{3,4,} = 0$). This amount is expressed by the term

$(CT_{4,1} - ST_{3,1})r_{3,1}$. The variables $QE_{i',i}$ can also be defined at the completion time $(CT_{4,1})$. Since all the amount of product 1 has been packaged up until the time point under consideration, the variable $QE_{1,4}$ should be equal to dm_1. On the other hand, only the line-shaded part of product 2 has been packed up until the time under consideration. This amount is expressed by the term $(CT_{4,1} - ST_{2,1})r_{2,2}$.

Mass balance constraints at the starting time of packing stage

As it has been mentioned above, mass balance constraints are also imposed at the starting time of packing stage of each product order.

$$QP_i \geq \sum_{i' \in I:\ f_i = f_{i'}} PI_{i,i'} - \sum_{i' \in I:\ f_i = f_{i'}:} PE_{i',i} \qquad \forall\, i \in I \tag{3.33}$$

$$QP_i \leq \sum_{v \in V} e_v YV_{i,v} \qquad \forall i \in I \tag{3.34}$$

The net stored amount (QP_i) at the starting of packing operation of product i is determined by constraints (3.33). The first term refers to the total imported amount, while the second term is related to the total consumed of the buffer tank. Constraints (3.34) guarantee that the stored amount (QP_i), will not exceed the related capacity of vessel v, (e_v). Similarly to the constraints (3.28)-(3.32), a set of inequalities are introduced to impose the required bounds on both variables $PI_{i,i'}$ and $PE_{i,i'}$.

$$PI_{i,i'} \geq dm_{i'}\left(1 - Z_{i,i'}\right) - dm_{i'}\left(1 - \sum_{v \in V}(XV_{i',i,v} + XV_{i,i',v})\right)$$
$$\forall i \in I, i' \in I : f_i = f_{i'} \tag{3.35}$$

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$$PI_{i,i'} \geq (ST_{i,2} - ST_{i',1})r_{i',1} - (d_i - pm_{i,2})\, r_{i',1}\left(1 - Z_{i,i'}\right) - (d_i - pm_{i,2})\, r_{i',1}\left(1 - \sum_{v \in V}(XV_{i',i,v} + XV_{i,i',v})\right) \quad \forall i \in I, i' \in I : f_i = f_{i'} \tag{3.36}$$

Constraints (3.35) and (3.36) determine variables $PI_{i,i'}$,by utilizing an auxiliary variable $Z_{i',i}$. According to constraints (3.16) and (3.17), variables $Z_{i,i'}$ take the value 1, only if a product order i' completes the formulation stage later than the starting time of packing operation of product i. As variables $Z_{i,i'}$ are equal to 1, it is implied that all the amount of product has been inserted into the buffer up until the time point under consideration. Thus, constraint (3.35) imposes the total amount of product i', $dm_{i'}$, as lower limit for the variable $PI_{i,i'}$. In the opposite case, constraint (3.36) guarantee that only a portion of the product order i has been filled into the storage vessel up until the considered time point. This amount is given by the term $(ST_{i,2} - ST_{i',1})r_{i',1}$. Similar to constraints (3.24) the term $(d_i - pm_{i,2})\, r_{i',1}$ plays the role of a big-M value.

An illustrative example for variable $PI_{i,i'}$ is shown in Figure 3.7, whereas the mass balance expression at the starting time of packing operation of product 4 is considered. Variables $Z_{4,2}$ and $Z_{4,3}$ are equal to 1 while variable $Z_{4,1}$ is zero. Although, all the produced amount of product 1 has been filled into the buffer tank, only the line-shaded portion of product 2 has been inserted up until the time under consideration. This portion is given by the term $(ST_{4,2} - ST_{2,1})r_{2,1}$. Since zero amount of product 3 has been filled into the tank so far, the related term, $(ST_{4,2} - ST_{3,1})r_{2,1}$, is negative and therefore the lower bound of variable $PI_{4,3}$ is forced to zero as well.

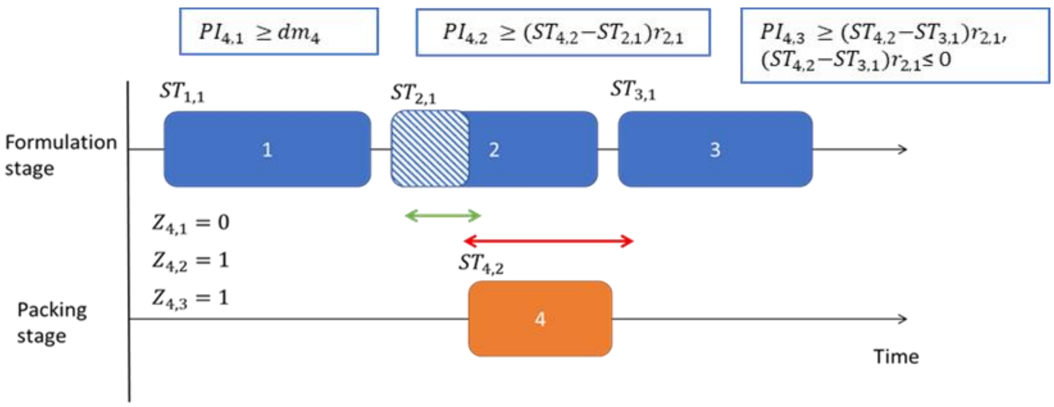

Figure 3.7 Indicative example of variable $PI_{i,i'}$

$$PE_{i,i'} \leq dm_{i'} P_{i',i,} \quad \forall i \in I, i' \in I : f_i = f_{i'} \tag{3.37}$$

$$PE_{i,i'} \leq (ST_{i,2} - ST_{i',2}) r_{i',2} + (d_i - pm_{i,2})\, r_{i',2} \left(1 - P_{i',i}\right) \tag{3.38}$$

$$\forall i \in I, i' \in I : f_i = f_{i'}$$

$$PE_{i,i'} \leq dm_{i'} \sum_{v \in V} (XV_{i',i,v} + XV_{i,i',v}) \quad \forall i \in I, i' \in I : f_i = f_{i'} \tag{3.39}$$

Constraints (3.37)- (3.39) determine variables $PE_{i,i'}$ .For this purpose, variable $P_{i',i,}$ is utilized. As it has been described earlier, $P_{i',i,}$ takes the value 1, only if product i' has completed its packing before product i. Constraints (3.37) and (3.39) ensure that the amount of $PE_{i,i'}$ does exceed the total amount of product i', ($dm_{i'}$). If a product order i' starts its packing after the packing operation of product order i, ($P_{i',i} = 0$), variables $PE_{i,i'}$ are forced to zero. This is also the case if products i and i' are not assigned to the same buffer tank ($\sum_v (XV_{i',i,v} + XV_{i,i',v}) = 0$). If a packing operation has not been completed by the specific time point, only a portion of product order i' is removed from the storage vessel. Thus, variable $PE_{i,i'}$ is further bounded by the term $(ST_{i,2} - ST_{i',2}) r_{i',2}$, as it is imposed by constraints (3.38). Similar to constraints (3.24) the term $(d_i - pm_{i,2})\, r_{i',1}$ plays the role of a big-M value in constraint (3.38).

An illustrative example for variable $PE_{i',i}$ is shown in Figure 3.8, where the mass balance constraints at the starting time of packing operation of product 4 are considered. Variables $P_{1,4}$ and $P_{2,4}$ are equal to 1 while variable $P_{3,4}$ takes a zero value. Even though all the produced amount of product 1 has been packaged, only the line-shaded portion of product 2 has completed its packing operation by the time under consideration. This portion is defined by the term $(ST_{4,2} - ST_{2,2}) r_{2,2}$. Furthermore, the packing operation of product 3 starts later and therefore the variable$PE_{i',i}$ is forced to zero.

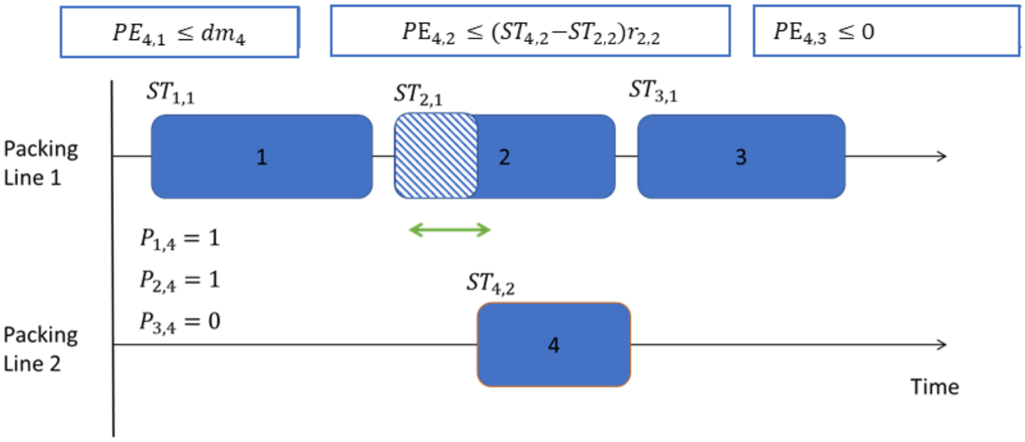

Figure 3.8 Indicative example of variable $PE_{i',i}$

Relationship between the starting and completion time of product orders

$$GP_i = ST_{i,2} - ST_{i,1} \quad \forall\, i \in I \tag{3.40}$$

$$GP_i \geq (pm_{i,1} - pm_{i,2}) \sum_{v \in V} YV_{i,v} \qquad \forall\, i \in I: pm_{i,2} < pm_{i,1} \tag{3.41}$$

$$GP_i \geq 0 \quad \forall\, i \in I: pm_{i,2} \geq pm_{i,1} \tag{3.42}$$

$$GP_i \leq g \sum_{v \in V} YV_{i,v} \qquad \forall\, i \in I \tag{3.43}$$

$$CT_{i,2} - ST_{i,1} \leq rs_i \quad \forall\, i \in I \tag{3.44}$$

$$CT_{i,2} \leq d_i \quad \forall\, i \in I \tag{3.45}$$

If the formulation stage is slower than the packing stage, it should be ensured that enough amount of product has already been filled into the buffer tank before the packing operation starts (Figure 3.9). Otherwise, the storage vessel will become empty and the packing process must be aborted. One way of satisfying this, is by utilizing the auxiliary variable GP_i, which expresses the difference of starting times between the two stages of product i. The variable GP_i has to be greater than the term $(pm_{i,1} - pm_{i,2})$, in case the production bottleneck is the formulation stage. On the other hand, if the formulation process operates in a time-consuming fashion, similar to the packing operation, this constraint is relaxed. Usually, depending on the specific industrial policies, an upper bound could be also set to the GP_i, or to the total residence time of a product, rs_i. in a buffer tank. If there is no limitation on the maximum residence time, the parameter rs_i have to be equal to the time horizon h. Constraints (3.43) also guarantee that if a product bypasses the storage tank, the process of the two stages will start simultaneously. Finally, constraints (3.45) ensure that each final product is produced earlier than its due date d_i.

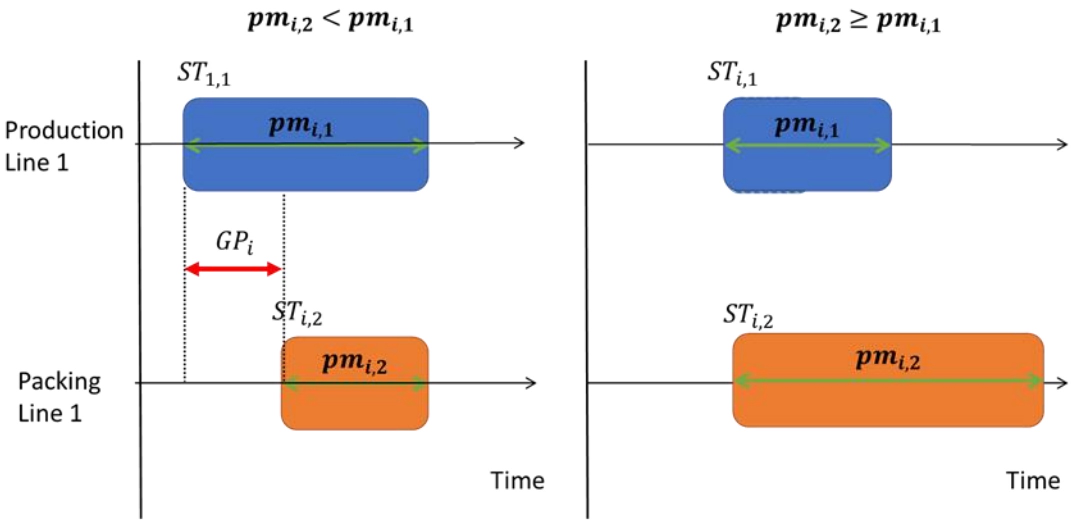

Figure 3.9 Definition of variable GP_i

Byproducts constraints

The constraints described in this subsection are referred to the formulation stage of the plant. Usually, several product-dependent changeovers take place among the production of different intermediate products. The majority of these changeovers is due to cleaning activities. In many cases, such as the production of detergents, the industrial practice does not permit cleaning with water, since water can affect the quality of the products. As a result, a significant amount of byproduct waste material is generated, which is usually stored in storage vessels and can be partially recycled into one of the next product orders without violating product quality specification.

The accumulated byproduct waste cannot exceed the storage capacity of the storage vessels. Explicit material balance constraints are introduced to prevent the overloading of storage vessels without using further binary variables or utilizing a discrete-time horizon.

As illustrated in Figure 3.10, during a changeover time an amount of byproduct is generated. Variables O_i express the amount of byproduct which is stored in the storage vessel at the end of the changeover which takes place after the production of intermediate product of production order i. A specific part of this amount (W_i) can be potentially recycled into one of the following orders. The recycled amount depends on the campaign length and the specific recipe of the intermediate product. If mixing is not allowed then the byproduct remains in the storage vessel. The remained amount can be recycled into the next production campaigns or remains into the vessel as the final waste (RW_j), in case there are no further product campaigns to recycle it.

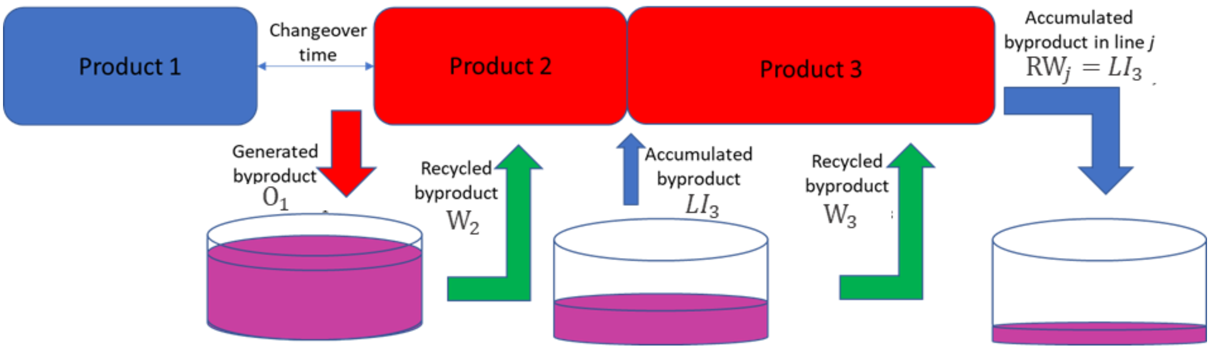

Figure 3.10 Byproducts recycling policy in a processing unit of formulation stage

$$O_i = LI_i + \sum_{i' \in I: i' \neq i} \sum_{j \in (JS_1 \cap JI_i \cap JI_{i'})} X_{i,i',j} n_{i,i'} r_{i',1} - W_i \quad \forall\, i \in I \tag{3.46}$$

Constraints (3.46) express the mass balances of byproduct storage vessels. The amount of byproduct waste O_i at the end of the changeover which takes place after the formulation of intermediate product of product order i, is equal to the previously accumulated material LI_i, plus the generated byproduct during the changeover, minus the amount which is recycled by the intermediate product of product order i, (W_i).

$$LI_i \leq O_{i'} + dm_i \left(1 - \sum_{j \in (JS_1 \cap JI_i \cap JI_{i'})} X_{i',i,j}\right) \quad \forall i \in I, i' \in I : i' \neq i \tag{3.47}$$

$$LI_i \geq O_{i'} - dm_i \left(1 - \sum_{j \in (JS_1 \cap JI_i \cap JI_{i'})} X_{i',i,j}\right) \quad \forall i \in I, i' \in I : i' \neq i \tag{3.48}$$

$$LI_i \leq iw_j \, Y_{i,j} + dm_i \sum_{i' \in IJ_j : i' \neq i} X_{i',i,j} \qquad \forall i \in I, j \in (JS_1 \cap JI_i) \tag{3.49}$$

$$LI_i \geq iw_j \, Y_{i,j} - dm_i \sum_{i' \in IJ_j : i' \neq i} X_{i',i,j} \qquad \forall i \in I, j \in (JS_1 \cap JI_i) \tag{3.50}$$

Constraints (3.47)-(3.50), define the accumulated amount of byproduct (LI_i), at the beginning of each product i. In particular, constraints (3.47) and (3.48), force variable LI_i equal to variable $O_{i'}$, only if intermediate of product i' is produced exactly before product i, ($X_{i',i,j} = 1$). Furthermore, the initial stored amount of byproduct of each unit (iw_j) is taken into account. Constraints (3.49) and (3.50) ensure that the accumulated amount of byproduct at the beginning of the first campaign of ($X_{i',i,j} = 0$), are equal to zero or equal to the initial byproduct amount (iw_j) at the beginning of the time horizon under consideration. The demand parameter dm_i is used as a big-M value in constraints (3.47-3.50)

$$W_i \leq dm_i \, a_i \qquad \forall i \in I \tag{3.51}$$

$$W_i \leq LI_i \quad \forall i \in I \tag{3.52}$$

Constraints (3.51) and (3.52) ensure that the amount of byproduct (W_i) which can be recycled into campaign i, must not exceed a specific maximum percentage of the total amount (dm_i). This percentage is defined by parameter a_i and depends on the quality specification of each intermediate product.

$$O_i \leq cp_j \, Y_{i,j} \qquad \forall i \in I, j \in (JS_1 \cap JI_i) \tag{3.53}$$

Constraints (3.53) guarantee that the stored amount of byproduct in the vessel of each unit, will not exceed the related capacity (CAP_j).

$$RW_j \geq O_i - cp_j \left(1 - Y_{i,j}\right) - cp_j \sum_{i' \in IJ_j \,:\, i' \neq i} X_{i,i',j} \qquad (3.54)$$

$\forall\, i \in I, j \in (\, JS_1 \cap\, JI_i\,)$

According to constraints (3.54), the final remained amount of byproduct waste in the storage vessel of a unit j (RW_j), is forced to be equal to the byproduct amount (O_i) of the last operated campaign ($Y_{i,j} = 1$, $X_{i,i',j} = 0$) at this unit. An inequality constraint is utilized, since variable RW_j is minimized by being part of cost minimization objective function. Industrial policies may also impose an upper bound on the remained unused amount of byproduct. In this case, a capacity constraint could also be used for variables RW_j. The maximum capacity parameter cp_j is used as a big-M value in constraints (3.54)

Objective function

$$\min\ TC = (\, cc \sum_{s \in S} \sum_{j \in JS_s} \sum_{i \in IJ_j} \sum_{i' \in IJ_j :\, i' \neq i} X_{i,i',j} n_{i,i',s} + + \qquad (3.55)$$

$$ic \sum_{s \in S} \sum_{i \in I} \sum_{i' \in I :\, i' \neq i} L_{i,i',s} + + pc \sum_{s \in S} \sum_{i \in I} T_{i,s} + \ bc \sum_{j \in JS_1} RW_j\,)$$

Objective (3.55) expresses the minimization of total costs. The first term represents the total changeover cost, while the second term expresses the total cost of idle times. The last two terms are related to the total production cost and the cost of the generated byproduct waste.

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3.4 Solution strategy

Due to the highly increasing demand and the high diversification of the product portfolio, in the vast majority of process industries, a plethora of different products are scheduled weekly. Although monolithic MILP approaches can generate optimal or nearly optimal solutions for small or medium-sized scheduling problems, they are not efficient for larger problem instances. To cope with this limitation, a decomposition-based solution algorithm is proposed. Similarly with previous research works (Kopanos, Méndez, and Puigjaner 2010; Elekidis, Corominas, and Georgiadis 2019) the solution strategy consists of a constructive and an improvement step. A brief schematic representation of the proposed solution strategy is illustrated in Figure 3.11.

3.4.1 Constructive step

The main idea of the constructive step is to decompose the initial problem into smaller subproblems which can be solved iteratively. At each iteration, a subset of product orders
$i \in I^{IN}$ is scheduled by using the proposed MILP model. Product orders are inserted based on a selected insertion policy. The related unit allocation variables, as well as the related sequencing variables, are fixed after each iteration. On the contrary, the timing variables and the sequencing variables of storage vessels remain free. Once all production orders have been inserted, an initial feasible solution is generated.

According to the selected insertion policy, products with the earliest due time are inserted first. The number of inserted products could vary, depending on the specific scheduling problem. Regarding the problem under consideration a 5-by-5 product insertion policy seems to be the optimal one, since by inserting more products, the solution is not improved while the computational cost is dramatically increased.

3.4.2 Improvement steps

To enhance the initial solution generated by the constructive step, two improvement steps are implemented sequentially. According to those, some production orders are extracted from the initial schedule and reinserted to further improve the solution. The marked products are exported from the initial schedule by relaxing the corresponding allocation and sequencing variables. The two proposed improvement steps are described below.

Improvement step 1

Usually, the synchronization of stages in continuous production plants is a challenging task and due to different production rates undesirable idle times are realized. Thus, the first improvement step is mainly focused on eliminating the idle times of the initial schedule. In particular, all production sequences that lead to idle times are identified and the related products $i \in I^{IDN}$ are reinserted. The MILP model is then solved and if the solution obtained is better than the solution of the constructive stage, the corresponding variables are updated.

Improvement step 2

To further improve the solution, part of the remaining products $i \in I^{REIN}$ is reinserted iteratively. In particular, 5 products are chosen lexicographically from set I and all related variables are relaxed in each iteration. At the same time, the remained product sequences that lead to idle times are detected as well and the related products i are also included into set $i \in I^{REIN}$ and reinserted. The MILP model is then solved at each iteration and if a better solution is found all variables and the objective function are updated.

Furthermore, industrial requirements usually impose an upper bound on the total solution time. Hence, an upper limit in the total CPU time, (lt), could be set as a stopping criterion. If the total CPU time exceeds this limit or all product orders have been reinserted, the algorithm is terminated, and the best solution found is reported. In this way, good quality solutions could be generated within reasonable computational times. A different stopping criterion could be set once the solution is improved by a specified percentage (in comparison with the previous stage). Finally, detailed pseudo-codes for the constructive and the improvement steps of the proposed solution strategy, are provided in in Appendix A.

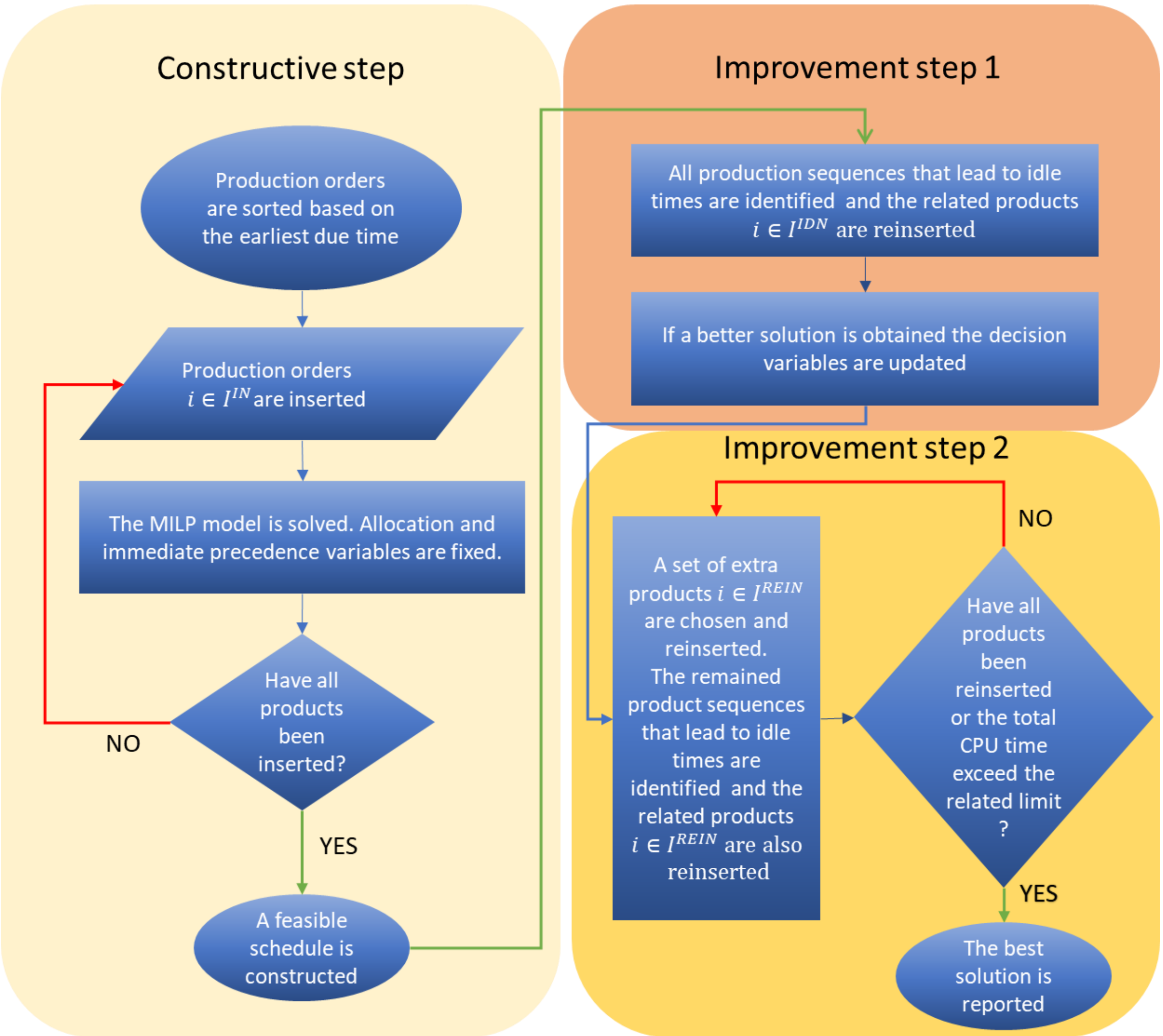

Figure 3.11 Schematic representation of the solution strategy

3.5 Case studies

To assess the applicability and the efficiency of the proposed MILP model and solution strategy, several problem instances are considered. Most problems simulate real-life industrial data of a large-scale consumer goods industry (Elekidis et al., 2019). The problem instances are based on 5 different cases, considering different product types and processing times. The data related to the first case are presented in Appendix B. Data for the rest of the cases under consideration are provided by Elekidis and Georgiadis, (2021). The proposed mathematical framework has been implemented in GAMS (General Algebraic Modeling System) and was solved using the IBM ILOG CPLEX

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12.0 solver with default settings and 8 threads, on 3.60 GHz Intel Core i7 7700 processor and 16 GB RAM.

3.5.1 Illustrative example

This problem consists of 15 final products, 3 packing lines, 3 production lines and 2 storage buffers. The time horizon of interest is 1 day (24 hours). Table 3.1 summarizes the capacities of storage vessels, while the individual cost coefficients are given in Table 3.2. For this example, the first 15 products of case 1 have been utilized.

Table 3.1 Capacity of vessels

Vessel	Capacity (kg)
Storage vessel 1	3000
Storage vessel 2	1600
Byproduct vessel 1	120
Byproduct vessel 2	160
Byproduct vessel 3	120

Table 3.2 Individual costs

Cost	Relative Money Units (RMU)
Changeover time cost	10 rmu/h
Idle time cost	30 rmu/h
Processing time cost	1 rmu/h
Byproduct waste cost	0.5 rmu/kg

The optimal schedule is depicted in Figure 3.12, corresponding to a total cost of 177.2857 relative money units (rmu). The cost distribution is presented via a pie chart in Figure 3.14. Since realistic cost data were not available, indicative cost values have been utilized. It is observed that the total idle time is forced to zero, since the higher cost is related to it. On the other hand, the largest percentage of the total cost, reflects the processing time. The buffer levels of the two intermediate storage tanks are illustrated in Figure 3.13.

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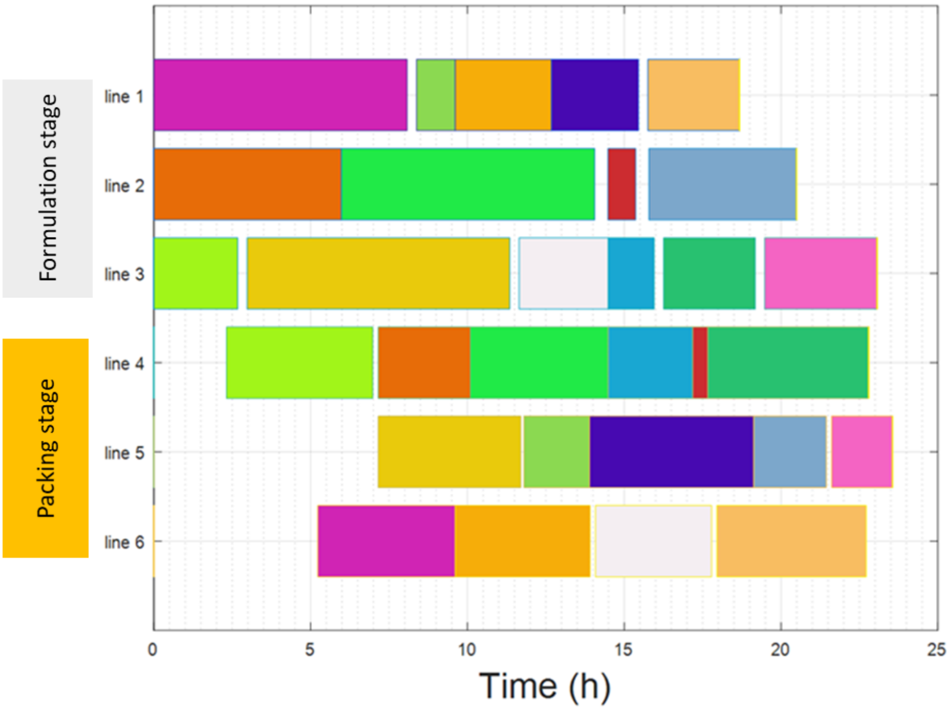

Figure 3.12 Gantt chart of the generated schedule for the illustrative example

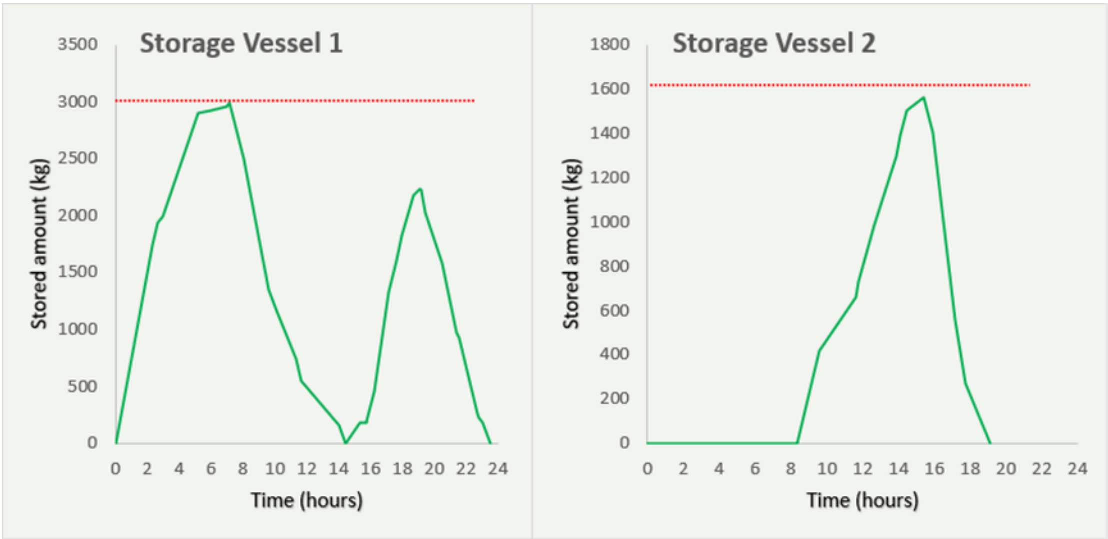

Figure 3.13 Total stored amount in buffer tanks

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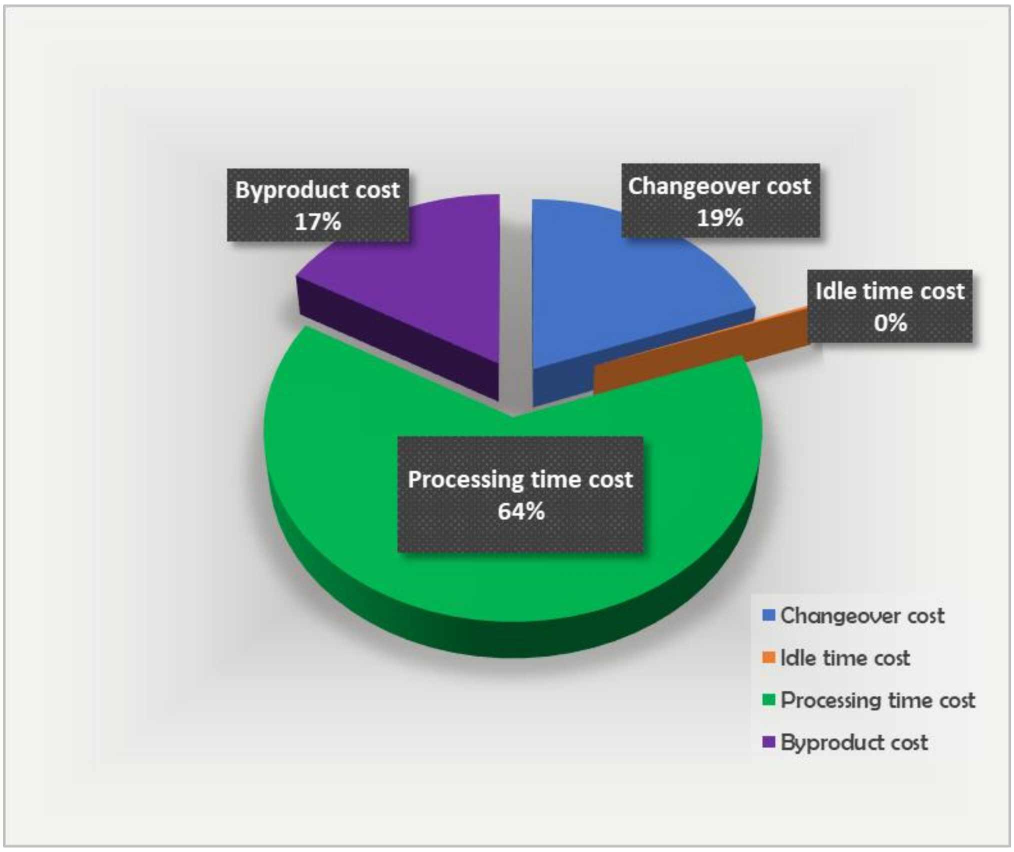

Figure 3.14 Cost distribution

Figure 3.15 illustrates the profile of generated amount of byproduct waste for each line. Due to the imposed byproduct cost, all the generated waste is recycled in lines 1 and 2. However, an amount of 20,5 kg remains in the storage tank of line 2. This amount represents 17% of the total costs, as shown in Figure 3.14.

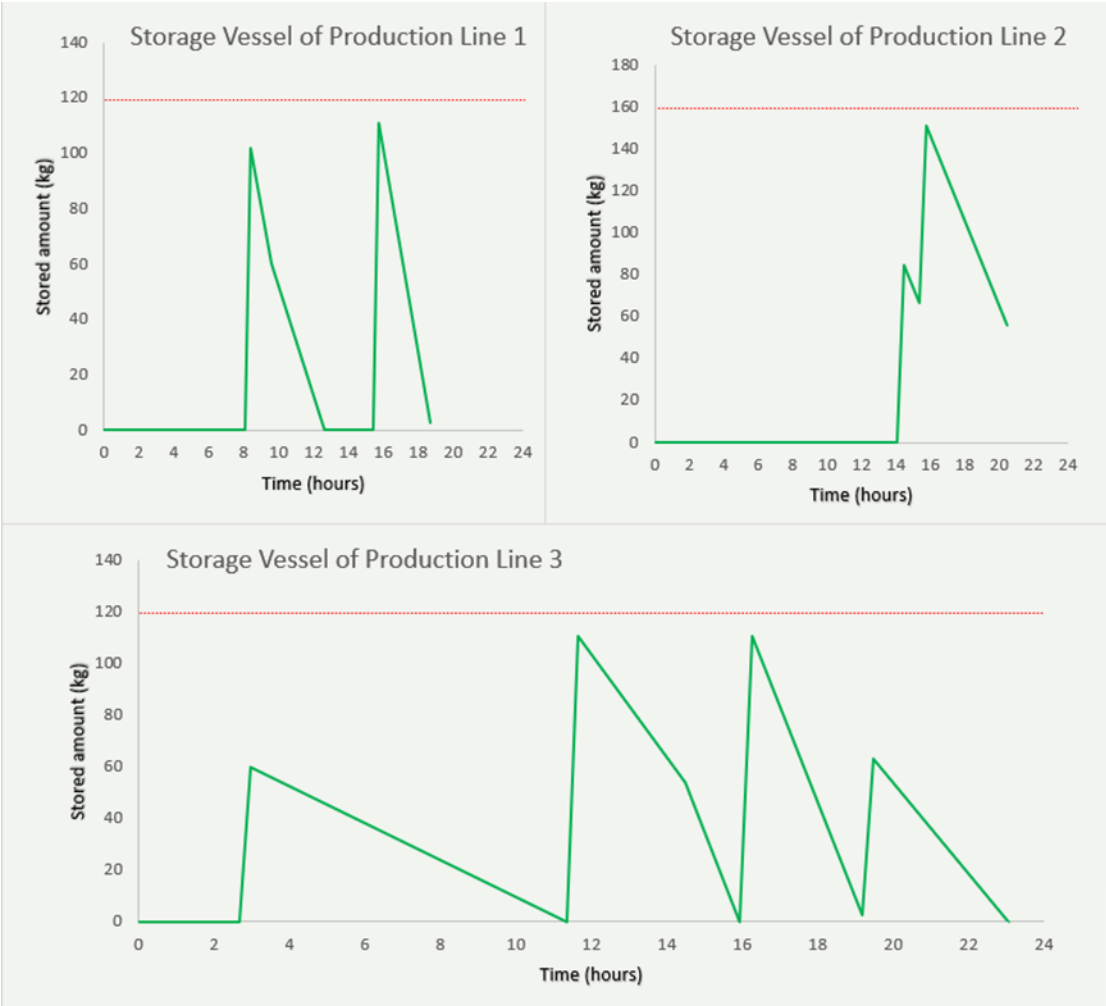

Figure 3.15 Total stored amount of byproduct in line tanks

3.5.2 Comparison between two plant layouts

A common issue in continuous process facilities is the necessity to synchronize the production rates of both stages. Usually, in continuous make-and-pack processes, the maximum production rate varies with the type of product and the slowest stage poses a varying production bottleneck. The utilization of intermediate storage tanks aims to improve the synchronization of production stages and thus, to increase the overall plant productivity.

To evaluate the benefits of the intermediate storage tanks, several case studies have been examined, by considering two different plant layouts: a decoupled layout with intermediate storage and a coupled layout without any storage. Both layouts use the same number of processing units (3 formulation and 3 packing lines) and their difference relies on the use of intermediate buffer tanks. The proposed MILP model and solution strategy have been used to solve several problem instances for the second plant layout (decoupled layout), while a single-stage, precedence-based MILP model, presented in section 2.3.1, has been used for the first plant layout (coupled layout). A total CPU time limit of 3600s has been imposed for all cases.

Since the majority of the make-and-pack facilities operates continuously 24 hours per day, the minimization of the total operational time often constitutes one of the main objectives (Elekidis et al., 2019).. The extra available time can be used to increase the total produced amount thus increasing the profits of the plant. Also, the reduction of the operational time is crucial since the extra time can be utilized to schedule more often maintenance tasks and it can provide additional flexibility if rescheduling decisions should be made. Often, cost data are not available in the process industries, since the calculation of individual costs is a time-consuming and challenging task. In those cases the minimisation of total operational time constitutes an alternative industrial objective (Elekidis et al., 2019). Thus, schedules have been generated for both layouts and detailed comparisons have been made between the total operational time of all processing units, which constitutes the objective function for this study. The total operational time includes the total processing time, the changeover time and the idle times of all production units. In other words, total operational time expresses the total makespan of each production unit.

The results are summarized in Table 3.3. It is observed that the intermediate storage vessels can provide significant flexibility, resulting in a notable improvement of the productivity of the plant. More specifically, productivity is increased, from 1.10% (case 4 with 25 products) to 33.75% (case 4 with 20 products). For problem instances with up to 50 products, optimal schedules have been generated for the coupled layout, by solving directly the monolithic MILP model (Elekidis et al., 2019). On the other hand, only problem instances with up to 20 products can be optimally solved for the decoupled layout by using the monolithic MILP model, while optimality gaps within the range of 5-10% are obtained within the CPU time limit, in cases with 25 products. Hence, the proposed decomposition strategy is utilized for the larger problem instances under consideration. As a result, smaller productivity gains are realised since suboptimal solutions are obtained in cases with 35 and 50 products. Problem instances with 70 products, have been solved by using the proposed decomposition strategies for both layouts. As it was expected, higher productivity gains are obtained for the decoupled layout in the range of 16.64% to 20.74%.

Table 3.3 Comparison between the total operational time (in hours) of the two layouts

Number of Products	Case	Decoupled plant layout		Coupled plant layout		Productivity gain (%)
		Objective (h)	CPU (s) / Optimality gap	Objective (h)	CPU (s) / Optimality gap	
15	Case 1	124.75	212 / 0%	170.13	112 / 0%	26.67%
	Case 2	82.07	226 / 0%	113.18	126 / 0%	27.49%
	Case 3	119.43	234 / 0%	136.92	134 / 0%	12.77%
	Case 4	100.22	267 / 0%	120.27	167 / 0%	16.67%
	Case 5	124.54	233 / 0%	173.05	133 / 0%	28.34%
20	Case 1	186.63	427 / 0%	225.63	127 / 0%	17.29%
	Case 2	127.34	462 / 0%	147.35	134 / 0%	13.58%
	Case 3	142.23	583 / 0%	170.55	183 / 0%	16.60%
	Case 4	104.22	692 / 0%	157.31	192 / 0%	33.75%
	Case 5	200.44	785 / 0%	240.54	185 / 0%	17.00%
25	Case 1	249.92	3600 / 5.6%	261.99	312 / 0%	4.61%
	Case 2	213.25	3600 / 9.7%	220.73	326 / 0%	3.39%
	Case 3	220.25	3600 / 6,2%	222.70	334 / 0%	1.10%
	Case 4	199.10	3600 / 6.4%	215.34	367 / 0%	7.54%
	Case 5	202.46	3600 / 5.1%	236.88	313 / 0%	14.53%
35	Case 1	355.34	299 /-	371.82	367 / 0%	4.43%
	Case 2	269.61	2603 /-	274.50	343 / 0%	1.78%
	Case 3	261.05	2603 /-	309.71	357 / 0%	15.71%
	Case 4	261.05	2603 /-	304.15	382 / 0%	14.17%
	Case 5	231.22	2603 /-	310.23	327 / 0%	25.47%
50	Case 1	422.14	2587 /-	442.70	562 / 0%	4.64%
	Case 2	288.92	2165 /-	335.24	578 / 0%	13.82%
	Case 3	362.20	1927 /-	377.41	614 / 0%	4.03%
	Case 4	366.59	1874 /-	374.48	582 / 0%	2.11%
	Case 5	342.46	2579 /-	381.97	627 / 0%	10.34%
70	Case 1	596.23	3484 /-	725.88	212 / -	17.86%
	Case 2	443.96	2462 /-	532.58	216 / -	16.64%
	Case 3	534.62	2194 /-	674.52	263 / -	20.74%
	Case 4	508.24	3295 /-	632.09	294 / -	19.59%
	Case 5	468.92	3571 /-	542.73	213 / -	13.60%

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3.5.3 Larger problem instances

In the vast majority of process industries, a large variety of final products is scheduled on a weekly or even on a daily basis. Thus, there is a strong necessity to develop efficient solution techniques, which can generate good quality schedules in low computational times for complex and challenging problems. To assess the efficiency and the applicability of the proposed modelling framework and solution strategy, a set of larger problem instances have been solved. The minimization of the total cost constitutes the objective. All cases consist of 3 packing lines, 3 production lines and 2 intermediate storage vessels. The individual cost coefficients are depicted in Table 3.2, for all cases. Results are summarized in Tables 3.4 and 3.5. A CPU time limit of 3600s is imposed to the algorithm, while a zero-optimality gap has been achieved in each iteration.

Table 3.4. Results for large problem instances – Comparison between the constructive and the improved solutions

Products			**Case 1**	**Case 2**	**Case 3**	**Case 4**	**Case 5**
50	TC	Constructive step	1326.87	707.91	768.06	665.73	699.87
		Improvement step	1301.67 (-1.9%)	675.35 (-4.6%)	745.40 (-2.9%)	622.43 (-6.5%)	648.14 (-7.3%)
	CPU time (s)	Constructive step	1684	2032	1753	2071	1719
		Total	2603	2746	2780	2649	2736
	Relaxed solution		975.75	436.73	489.13	397.14	397.14
60	TC	Constructive step	2561.49	679.86	946.74	878.15	910.50
		Improvement step	1999.60 (-21.9%)	664.88 (-2.2%)	919.96 (-2.8%)	827.52 (-5.7%)	849.81 (-6.6%)
	CPU time (s)	Constructive step	2103	2124	2101	1839	2099
		Total	2639	2800	2632	2783	2635
	Relaxed solution		1299.35	404.07	498.95	477.72	479.96

**TC=Total cost in monetary units*

Table 3.5. Results for large problem instances – Comparison between the constructive and the improved solutions

Products			**Case 1**	**Case 2**	**Case 3**	**Case 4**	**Case 5**
70	TC	Constructive step	3505.94	811.47	1091.66	1087.62	1124.40
		Improvement step	3378.55 (-3.6%)	794.67 (-2.1%)	1064.86 (-2.8%)	1045.75 (-3.8%)	1056.92 (-6.0%)
	CPU time (s)	Constructive step	2155	2467	2633	2686	2792
		Total	3600	3365	3600	3600	3600
	Relaxed solution		2297.04	589.92	677.62	701.11	786.39
100	TC	Constructive step	5455.10	1499.83	1568.30	1870.55	1939.96
		Improvement step	5117.08 (-6.6%)	1415.93 (-5.5%)	1558.30 (-0.6%)	1857.71 (-0.6%)	1847.83 (-4.7%)
	CPU time (s)	Constructive step	2805	2895	2907	2865	2898
		Total	3600	3600	3600	3600	3600
	Relaxed solution		3859.82	915.61	1046.52	1192.75	1126.36

**TC=Total cost in monetary units*

The proposed improvement step leads to notable benefits in terms of total cost reduction. In particular, the total cost is reduced from 0.64% (case 3 with 100 products) up to 21.9% (case 1 with 60 products). The relaxed solution of each problem is also presented in Table 3.4 and Table 3.5 in order to provide a bound on the value of the optimal objective. The computational time of both stages is provided as well. The improvement is mainly achieved by reducing the idle time cost as it illustrated in Tables 3.6 – 3.9, where the individual costs of each problem instance are presented.

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Table 3.6 Results for large problem instances – Comparison between the constructive and the improved solutions for cases with 50 products

Case	Algorithm step	TC*	COC*	ITC*	PTC*	WC*
Case 1	Constructive step	1326.87	210.10	651.79	385.47	79.50
	Improvement step	1301.67 (-1.90%)	221.80 (+5.28%)	614.89 (-6.00%)	385.47 (0.00%)	79.50 (0.00%)
Case 2	Constructive step	707.91	161.50	136.32	256.96	153.13
	Improvement step	675.35 (-4.6%)	162.80 (+0.80%)	127.23 (-6.67%)	256.96 (0.00%)	128.37 (-16.17%)
Case 3	Constructive step	768.06	174.50	169.72	295.39	128.45
	Improvement step	745.40 (-2.95%)	186.20 (+6.70%)	153.12 (-9.78%)	289.84 (-1.88%)	116.24 (-9.50%)
Case 4	Constructive step	665.73	168.26	86.85	279.82	130.80
	Improvement step	622.43 (-6.50%)	179.1 (+6.44%)	40.56269 (-53.30%)	279.82 (0.00%)	122.9489 (-6.00%)
Case 5	Constructive step	699.87	179.00	92.39	297.68	130.79
	Improvement step	648.14 (-7.39%)	179.10 (+0.06%)	40.56 (-56.10%)	297.68 (0.00%)	130.79 (0.00%)

**TC=Total cost, COC=Changeover cost, ITC=Idle time cost, PTC=Processing time cost, WC=Waste cost*

***The costs represent monetary units*

Table 3.7 Results for large problem instances – Comparison between the constructive and the improved solutions for cases with 60 products

Case	Algorithm step	TC*	COC*	ITC*	PTC*	WC*
Case 1	Constructive step	2561.49	221.10	1812.12	470.69	57.58
	Improvement step	1999.60 (-21.90%)	231.90 (+4.66%)	1224.17 (-48.03%)	470.69 (0.00%)	72.84 (+20.95%)
Case 2	Constructive step	679.86	201.60	148.90	329.36	0.00
	Improvement step	664.88 (-2.2%)	210.00 (+4.2%)	123.70 (-16.9%)	329.36 (0.00%)	0.00 (0.00%)
Case 3	Constructive step	946.74	195.50	377.27	373.96	0.0
	Improvement step	919.96 (-2.83%)	211.90 (+8.39%)	334.07 (-11.45%)	373.96 (0.00%)	0.00 (0.00%)
Case 4	Constructive step	878.15	196.74	309.96	366.30	5.16
	Improvement step	827.52 (-5.77%)	229.80 (+16.80%)	248.55 (-19.81%)	344.32 (-6.00%)	4.85 (-6.00%)
Case 5	Constructive step	910.50	209.3	329.74	366.30	5.16
	Improvement step	849.81 (-6.67%)	229.80 (9.79%)	248.55 (-24.62%)	366.30 (0.00%)	5.16 (0.00%)

**TC=Total cost, COC=Changeover cost, ITC=Idle time cost, PTC=Processing time cost, WC=Waste cost*

***The costs represent monetary units*

Table 3.8 Results for large problem instances – Comparison between the constructive and the improved solutions for cases with 70 products

Case	Algorithm step	TC*	COC*	ITC*	PTC*	WC*
Case 1	Constructive step	3505.94	299.00	2592.56	541.69	72.70
	Improvement step	3378.55 (-3.6%)	304.60 (+1.84%)	2459.57 (-5.41%)	541.69 (0.00%)	72.70 (0.00%)
Case 2	Constructive step	811.47	242.00	159.64	378.25	31.58
	Improvement step	794.67 (-2.07%)	250.40 (+3.47%)	134.44 (-15.79%)	378.25 (0.00%)	31.58 (0.00%)
Case 3	Constructive step	1091.66	239.30	391.37	433.40	27.58
	Improvement step	1064.86 (-2.83%)	255.70 (+6.85%)	348.17 (-11.04%)	433.40 (0.00%)	27.58 (0.00%)
Case 4	Constructive step	1087.62	243.65	332.66	421.32	89.98
	Improvement step	1045.75 (-3.85%)	259.50 (+6.51%)	347.22 (-4.38%)	421.32 (0.00%)	17.71 (-80.32%)
Case 5	Constructive step	1124.40	259.20	353.90	421.32	89.98
	Improvement step	1056.92 (-6.00%)	255.60 (-1.39%)	344.77 (-2.58%)	421.32 (0.00%)	35.22 (-60.86%)

**TC=Total cost, COC=Changeover cost, ITC=Idle time cost, PTC=Processing time cost, WC=Waste cost*

***The costs represent monetary units*

Table 3.9 Results for large problem instances – Comparison between the constructive and the improved solutions for cases with 100 products

Case	Algorithm step	TC*	COC*	ITC*	PTC*	WC*
Case 1	Constructive step	5455.10	422.29	4193.11	757.67	82.03
	Improvement step	5117.08 (-6.61%)	409.20 (+3.20%)	3868.19 (8.41%)	757.67 (0.00%)	82.03 (0.00%)
Case 2	Constructive step	1499.83	381.40	397.37	532.52	188.54
	Improvement step	1415.93 (-5.59%)	391.32 (+2.60%)	381.63 (-3.96%)	532.52 (0.00%)	110.46 (-41.41%)
Case 3	Constructive step	1568.30	342.10	481.39	608.29	136.53
	Improvement step	1558.30 (-0.64%)	350.10 (+2.34%)	463.39 (-3.74%)	608.29 (0.00%)	136.53 (0.00%)
Case 4	Constructive step	1870.55	364.53	783.24	549.87	172.92
	Improvement step	1857.71 (-0.69%)	389.90 (+6.96%)	731.33 (-6.63%)	584.96 (+6.38%)	151.51 (-12.38%)
Case 5	Constructive step	1939.96	387.80	783.24	584.96	183.95
	Improvement step	1847.83 (-4.75%)	391.10 (+0.85%)	720.26 (-8.04%)	584.96 (0.00%)	151.51 (-17.63%)

**TC=Total cost, COC=Changeover cost, ITC=Idle time cost, PTC=Processing time cost, WC=Waste cost*

***The costs represent monetary units*

Figure 3.16 presents the Gantt chart of an illustrative example focusing on the improvement step. The first Gannt chart illustrates the initial solution, obtained by the constructive step. The first feasible solution can be further improved by implementing an additional improvement step, as it is shown in the second Gantt chart. In particular, since the improvement step aims to decrease the total cost, unnecessary idle times are detected, and better solutions are obtained by reinserting a set of products. In the example of Figure 3.16 an idle time is detected in the initial schedule in line 5. The idle time is eliminated by reinserting a set of products via the improvement step, as it is shown in the second Gannt chart.

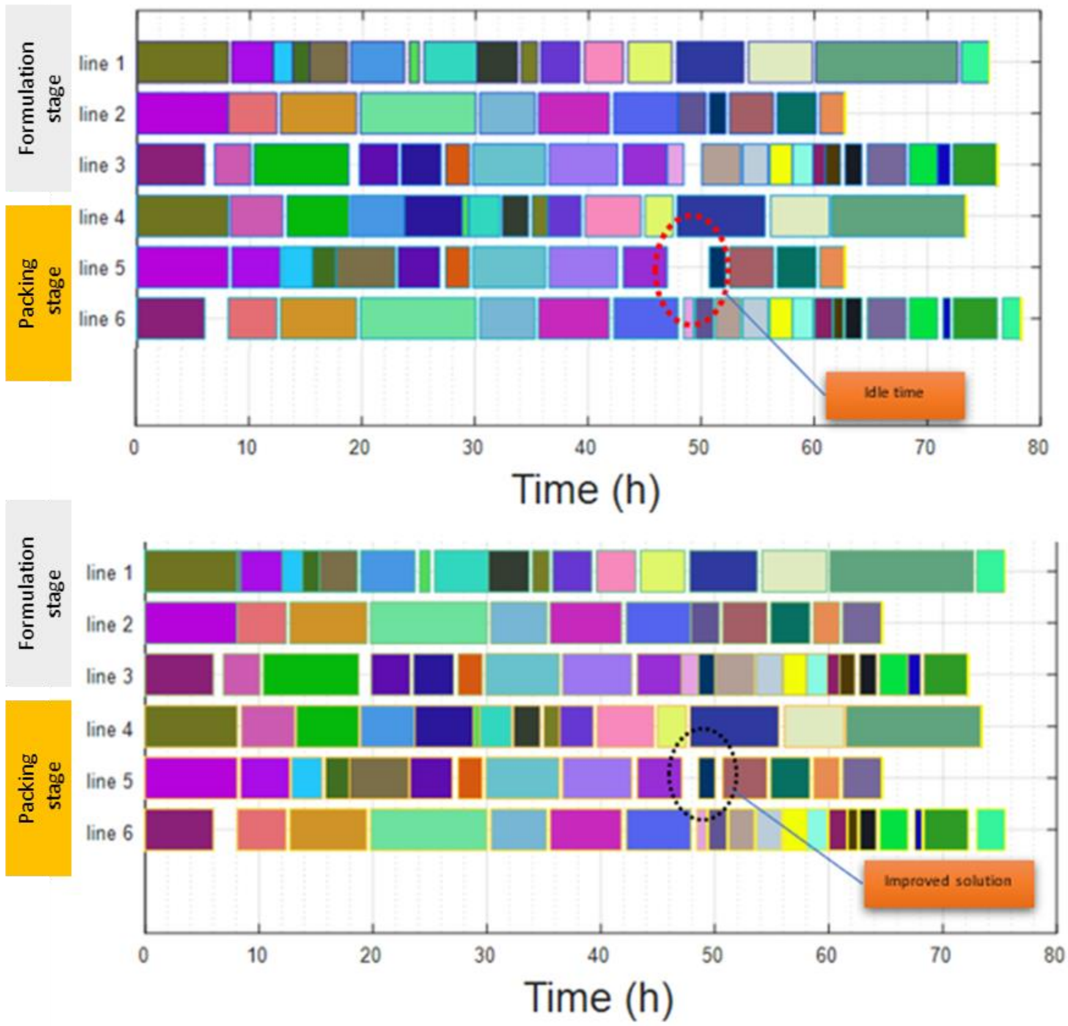

Figure 3.16 Indicative Gannt chart of the schedules of constructive and improvement steps

Furthermore, in order to assess the quality of solutions obtained using the proposed solution algorithm, a detailed comparison of the monolithic MILP model and the proposed solution strategy is presented in Table 3.10. It is observed that for problem instances with up to 25 products near optimal solutions can be generated by using the proposed solution algorithm in small computational times. For larger problem instances, even a feasible solution cannot be generated using the monolithic MILP model under the specified time limits.

Table 3.10 Comparison between the monolithic MILP model and the proposed solution strategy considering the minimization of total cost

Number of Products	**Case**	**MILP**			**Solution approach**	
		Objective (rmu)	Optimality gap	CPU time (s)	Objective (rmu)	CPU time (s)
15	Case 2	102.68	0.00%	209	119.49	109
	Case 3	119.43	0.00%	217	128.56	117
	Case 4	107.09	0.00%	198	137.27	98
	Case 5	124.54	0.00%	238	139.68	100
20	Case 2	152.42	0.00%	424	156.96	256
	Case 3	157.19	0.00%	359	171.79	267
	Case 4	105.39	0.00%	533	199.97	198
	Case 5	200.44	0.00%	686	204.97	238
25	Case 2	311.16	1.29%	3600	313.36	288
	Case 3	330.60	0.67%	3600	350.56	296
	Case 4	378.65	6.34%	3600	417,12	263
	Case 4	332.48	7.83%	3600	378.27	257

3.5.4 Comparison between different storage policies

The proposed MILP model allows the implementation of flexible-storage policies, according to which each intermediate product can be stored temporarily in a buffer tank or transferred directly to the packing stage bypassing the storage tanks. To assess potential benefits of this flexible-storage policy, two problem instances are considered, in which different storage policies are compared. Both cases include 3 packing lines and 3 production lines. Except from the aforementioned flexible-storage policy, an obligatory-storage policy is also considered. According to this, all product orders are stored obligatorily into an intermediate buffer tank before their packing. The results are summarized in Table 3.11 for problem instances with 50 products and in Table 3.12 for problem instances with 70 products.

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Table 3.11. Results of different storage policies in problem instances with 50 products

Case	Storage policy	Buffer tanks	TC*	COC*	ITC*	PTC*	WC*
Case 1	Obligatory storage	2	4604.94	387.98	3625.01	517.97	73.99
	Obligatory storage	3	3320.62 (-20.64%)	331.64 (-12.5%)	2724.56 (-24.8%)	517.97 (0.00%)	72.70 (-1.74%)
	Flexible storage	2	3378.55 (-26.63%)	304.60 (-21.4%)	2459.57 (-32.1%)	541.69 (+4.58%)	72.70 (-1.74%)
Case 2	Obligatory storage	2	769.74	199.41	200.84	239.14	130.35
	Obligatory storage	3	689.86 (-10.38%)	174.29 (-12.6%)	147.43 (-26.5%)	239.14 (0.00%)	129.00 (-1.0%)
	Flexible storage	2	675.35 (-12.26%)	162.8 (-18.3%)	127.23 (-36.6%)	256.96 (+7.45%)	128.37 (-1.52%)
Case 3	Obligatory storage	2	896.09	240.48	232.78	289.84	133.00
	Obligatory storage	3	778.82 (-13.09%)	200.75 (-16.5%)	163.83 (-29.6%)	289.84 (0.00%)	124.41 (-6.46%)
	Flexible storage	2	745.4 (-16.82%)	186.2 (-22.7%)	153.12 (-34.2%)	289.84 (0.00%)	116.24 (-12.6%)
Case 4	Obligatory storage	2	687.20	243.91	70.79	248.49	124.02
	Obligatory storage	3	638.62 (-7.07%)	195.30 (-19.9%)	48.12 (-32.0%)	271.99 (+9.46%)	123.22 (-0.64%)
	Flexible storage	2	622.43 (-9.4%)	179.1 (-26.5%)	40.56 (-42.7%)	279.82 (+12.61%)	122.94 (-0.86%)
Case 5	Obligatory storage	2	707.32	229.29	70.91	271.26	135.86
	Obligatory storage	3	662.93 (-6.28%)	191.65 (-16.4%)	48.15 (-32.1%)	291.07 (+7.31%)	132.06 (-2.81%)
	Flexible storage	2	648.14 (-8.37%)	179.10 (-21.9%)	40.56 (-42.8%)	297.68 (+9.74%)	130.79 (-3.73%)

**TC=Total cost. COC=Changeover cost. ITC=Idle time cost. PTC=Processing time cost. WC=Waste cost*

***The costs represent monetary units*

Table 3.12 Results of different storage policies for cases with 70 products

Case	Storage policy	Buffer tanks	TC*	COC*	ITC*	PTC*	WC*
Case 1	Obligatory storage	2	4971.26	372.64	3990.22	532.06	76.34
	Obligatory storage	3	3706.39 (-25.44%)	318.98 (-14.40%)	2777.19 (-30.4%)	536.32 (+0.82%)	73.90 (-3.21%)
	Flexible storage	2	3378.55 (-32.04%)	304.60 (-18.26%)	2459.57 (-38.3%)	541.69 (+1.81%)	72.70 (-4.77%)
Case 2	Obligatory storage	2	942.91	321.03	240.07	350.23	31.58
	Obligatory storage	3	825.49 (-12.45%)	274.80 (-14.4%)	167.09 (-30.3%)	353.03 (+0.78%)	30.57 (-3.27%)
	Flexible storage	2	794.67 (-15.72%)	250.40 (-22.1%)	134.44 (-44.6%)	378.25 (+8.04%)	31.58 (0.00%)
Case 3	Obligatory storage	2	1458.74	309.00	693.84	426.07	29.82
	Obligatory storage	3	1138.81 (-21.93%)	261.03 (-15.53%)	417.30 (-39.86)	432.67 (+1.55%)	27.80 (-6.77%)
	Flexible storage	2	1064.86 (-27.12%)	255.70 (-17.25%)	348.17 (-49.8%)	433. 67 (+1.55%)	27.58 (7.52%)
Case 4	Obligatory storage	2	1314.69	244.35	631.31	421.32	17.71
	Obligatory storage	3	1083.95 (-17.55%)	240.88 (-1.42%)	404.04 (-36.1%)	421.32 (0.00%)	17.71 (0.00%)
	Flexible storage	2	1045.75 (-20.46%)	259.50 (+6.21%)	347.22 (-45.0%)	421.32 (0.00%)	17.71 (0.00%)
Case 5	Obligatory storage	2	1190.52	283.18	450.80	421.32	35.22
	Obligatory storage	3	1094.52 (-8.06%)	271.12 (-4.26%)	366.86 (-18.6%)	421.32 (0.00%)	35.22 (0.00%)
	Flexible storage	2	1056.92 (-11.2%)	255.60 (-9.74%)	344.77 (-23.5%)	421.32 (0.00%)	35.22 (0.00%)

**TC=Total cost. COC=Changeover cost. ITC=Idle time cost. PTC=Processing time cost. WC=Waste cost*

***The costs represent monetary units*

Results illustrate clearly a significant reduction in the total cost, by implementing a flexible-storage policy. In particular, the total cost is decreased by 26.63% in cases with 50 products, while a decrease of 32,04% is realized in cases with 70 products. It is noticed that the improvements are mainly due to the idle-time cost reduction.

3.5.5 Consideration of byproducts

The impact of byproduct recycling is studied here, using the problem instances with 50, 60, 70 and 100 products form case 1. The capacity of byproducts vessel tanks is equal to 160 kg and the stored amount should not exceed this limit. Figure 3.17 shows, the total amount of recycles for each case. It is noticed that the byproduct recycles constitute a significant percentage of the total produced amount, which ranges from 6.1% (Case 1 with 50 products) to 7.57% (Case 4 with 100 products). It is therefore clear that the usage of this policy leads to better utilization of raw materials and significant reduction of material cost.

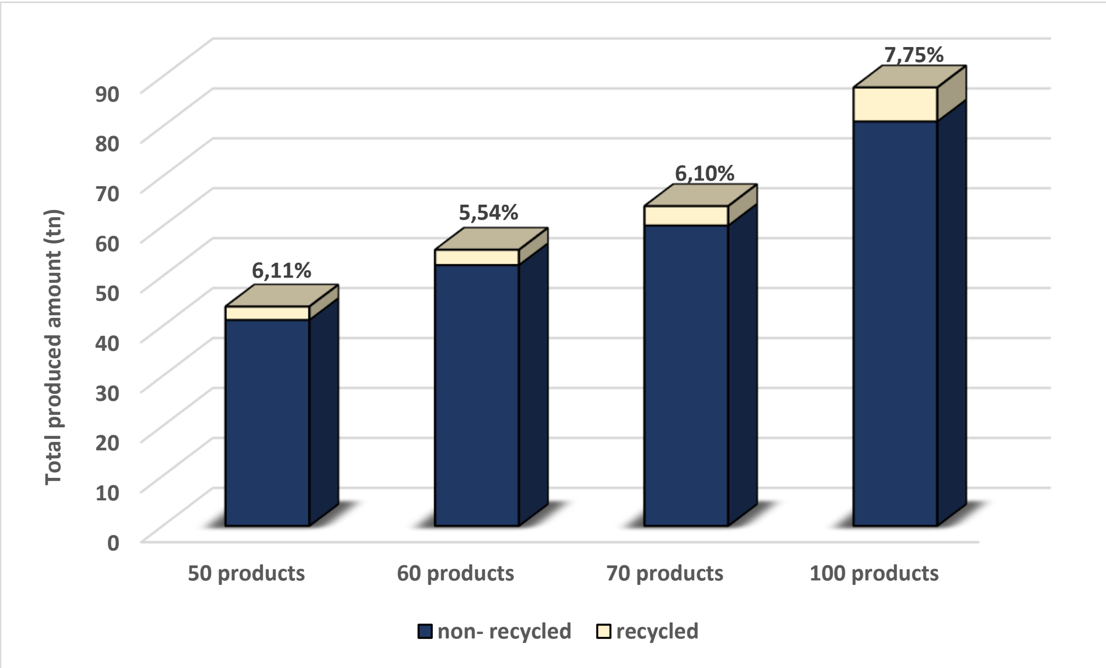

Figure 3.17 Recycled amount

Furthermore, Case 1 has been solved with and without the proposed byproducts constraints. It is noticed that the generated waste violates the storage capacity in all vessels if capacity constraints are ignored. On the other hand, storage limitations are fully respected by considering the proposed byproduct constraints. The profile of stored amount for both cases is illustrated in Figure 3.18 and Figure 3.19.

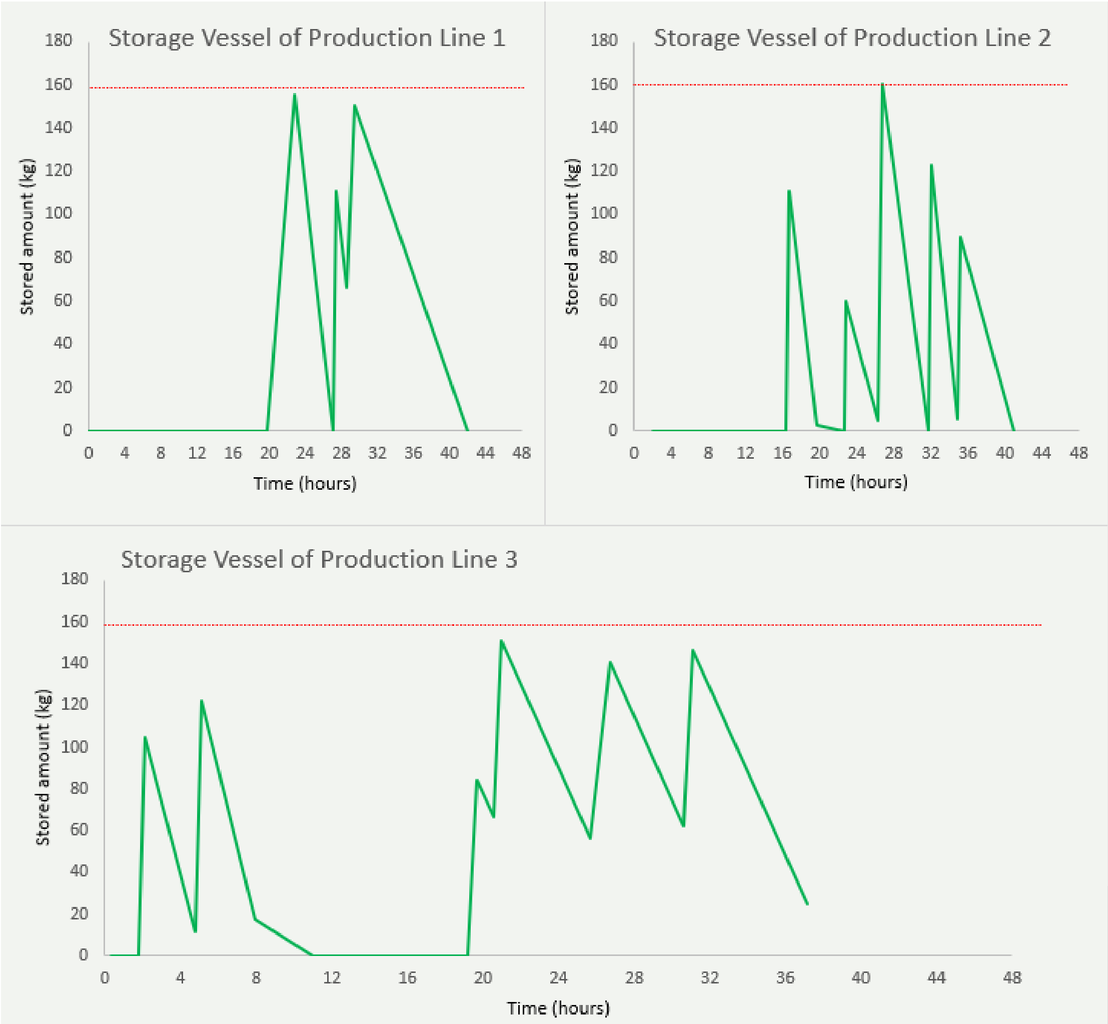

Figure 3.18 Case 1 - Total stored amount of byproduct in tanks considering byproducts constraints

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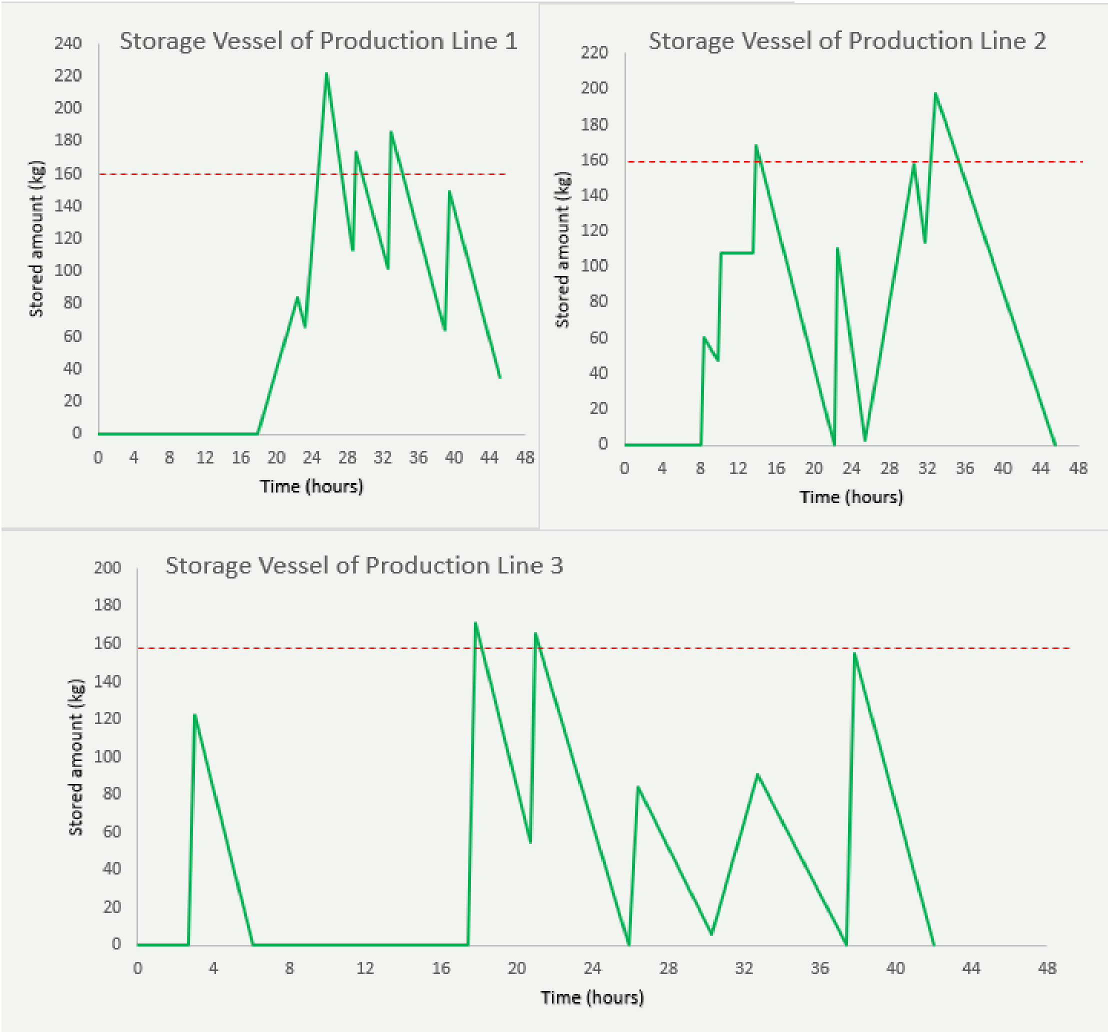

Figure 3.19 Case 1 - Total stored amount of byproduct in tanks without considering byproducts constraints

3.6 Conclusions

This chapter presents a precedence-based MILP model framework, for the scheduling of continuous, make-and-pack industries. Intermediate buffers are considered to achieve a better synchronization between the two production stages. Instead of using a discrete time horizon, a set of auxiliary binary variables are introduced, to correctly handle mass balance constraints. A salient feature of the modelling framework is the recycling of byproducts waste, to achieve a better utilization of raw material and resources. For the solution of large problem instances, a two-stage decomposition algorithm is proposed. Several case studies have been solved, to consider the application of the proposed

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modelling frameworks and solution strategy. Results illustrate significant improvements in the economic operation of the plant. To evaluate the benefits of intermediate storage tanks, different plant layouts have been studied. The intermediate storage tanks provide better synchronization of the production stages and lead to significant productivity gains, while flexible-storage policies result in higher cost savings in comparison with obligatory storage. The proposed two-stage decomposition strategy can provide good-quality schedules for large-scale problems and can potentially constitute an important tool for engineers to derive fast and rigorous scheduling decisions in a dynamic environment. Further extension of the proposed optimization-based approach seems a promising research task. Future works are envisaged to focus on extending the proposed approach, by considering multiple production stages with flexible storage tanks. Moreover, another direction for future extension would be the development of an integrated planning and scheduling optimization framework, by including lot-sizing decisions and inventory constraints.

Nomenclature

MILP model

Indices/sets

$i, i' \in I$	Production orders
$j \in J$	Production units
$s \in S$	Processing stages
$v \in V$	Storage vessels

Subsets

JI_i	Processing units $j \in J$ available to process production orders $i \in I$, ($JI_i \subseteq J$)
IJ_j	production orders $i \in I$ that can be processed by processing units $j \in J$, ($IJ_j \subseteq I$)
JS_s	Available processing units $j \in J$ to process stage $s \in S$, ($JS_S \subseteq J$)

Parameters

a_i	upper percentage of the total amount of product i that can be recycled
cc	Changeover cost
cp_j	Capacity of byproduct vessel of unit j
d_i	due date for product order i
dm_i	Demand of product i
e_v	Capacity of vessel v
f_i	Recipe of product i
g	maximum difference of starting times between the two stages of the products
h	The time horizon under consideration
ic	Idle-time cost
iw_j	The initial stored amount of byproduct at the storage tank of each processing unit j

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M A big number

$n_{i,i',s}$ changeover time between two consecutive production orders i and i' at stage s

pc production time cost

pl_i Maximum processing time of product i in both stages

$pm_{i,s}$ Minimum processing time of product i at stage s

$r_{i,s}$ Maximum production rate of product i at stage s

rs_i Maximum residence time of a product i at a storage tank

wc Byproduct cost

Continuous Variables

$CT_{i,s}$ Completion time of product *i* at production stage *s*

GP_i Difference of starting times between the two stages of product i

$L_{i,i',s}$ Idle time between product *i* and i' at production stage *s*

LI_i Accumulated amount of byproduct waste in the unit that operates product *i* at the starting time of formulation stage

O_i Accumulated amount of byproduct waste in the unit that operates product *i* at the ending time of formulation stage

$PE_{i',i}$ Exported amount of product i' in a storage vessel up until the starting time of packing stage of product *i*

$PI_{i,i'}$ Inserted amount of product i' in a storage vessel up until the

	starting time of packing stage of product *i*
Q_i	Stored amount of product *i*
$QE_{i',i}$	Exported amount of product i'in a storage vessel up until the end of formulation stage of product *i*
$QI_{i',i}$	Inserted amount of product i' in a storage vessel up until the end of formulation stage of product *i*
QP_i	Stored amount up until the starting time of packing stage of product *i*
QT_i	Stored amount up until the end of formulation stage of product *i*
RW_j	Remained amount of byproduct waste at the end of time horizon in unit *j*
$ST_{i,s}$	Starting time of product, *i* at production stage *s*
$T_{i,s}$	Processing time of product *i* at production stage *s*
TC	Total cost
W_i	Amount of waste which is recycled by product *i*

Binary Variables

$K_{i,i'}$	Takes the value 1 only if a production order *i* completes formulation earlier than the completion time of the formulation stage of production order i'.
$P_{i,i'}$	Takes the value 1 only if a product production order *i* starts packing earlier than the starting time of the packing stage of production order i'.

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$XV_{i,i',v}$	Takes the value 1 only if production order i stored before production order i' at in the storage tank v
$X_{i',i,j}$	Takes the value 1 only if production order i is processed exactly before order i' in unit j
$Y_{i,j}$	Takes the value 1 only if a production order i is allocated to unit j
YO_i	Takes the value 1 only if a production order i starts packing later than the completion time of its formulation stage
$YV_{i,v}$	Takes the value 1 only if a production order i is allocated to vessel v
$Z_{i,i'}$	Takes the value 1 only if a production order i starts packing earlier than the completion time of the formulation stage of production order i'

Solution strategy

Indices/sets

$i \in I^{IN}$	Subset of production orders, which are inserted into the schedule of the constructive step of solution strategy ($I^{IN} \subseteq I$)
$i \in I^{IDN}$	Subset of production orders, which are reinserted during the first improvement step of solution strategy, since an idle time is detected before or after its processing ($I^{IDN} \subseteq I$)
$i \in I^{REIN}$	Subset of production orders, which are reinserted during the second improvement step of solution strategy ($I^{REIN} \subseteq I$)

Parameters

pos_i	The relative position of element i in set I
lt	The total CPU time limit of solution algorithm

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4

Optimal Contract Selection for Contract Manufacturing Organizations in the Pharmaceutical Industry Under Demand Uncertainty

4.1 Introduction

Over the past few years, large R&D pharmaceutical companies have increasingly outsourced non-core activities, such as manufacturing, to Contract Manufacturing Organisations (CMOs), which are companies without their own product portfolio. Contract Manufacturing Organizations utilize their facilities to manufacture products for multinational pharmaceutical companies on a contract basis. This policy enables R&D multinationals to reduce costs and emphasise on drug discovery and marketing, which are the key parts for their value chain. Typically, drug development is a time-consuming process, as it takes at least 10 years on average for a new medicine to be in the marketplace. Additionally, demand of newly developed pharmaceutical products is usually highly uncertain. Lower drug efficacy can affect the demand and total sales, while in the worst case, it can lead to the suspension or even the withdrawal of drugs. Under this dynamic and uncertain environment, CMOs must define which contracts to accept to maximize their profit while considering their risk tolerance (Marques et al., 2020).

Although several research contributions have been focused on the scheduling of pharmaceutical industries and on the planning of clinical trials (Sundaramoorthy et al., 2012), the contract selection problem of Contract Manufacturing Organizations has not been considered in the open literature. Hence, in this chapter an integrated tactical planning and medium-term scheduling framework is proposed for the optimal contract appraisal problem of Contract Manufacturing Organizations in the secondary pharmaceutical industry under demand uncertainty.

First, an aggregated MILP-based planning model is proposed, including material balances, time horizon and allocation constraints. A general precedence MILP model for the scheduling of multistage, multiproduct, batch industries is also proposed. The production targets are defined in the planning decision level using a rolling horizon framework, while the scheduling MILP model makes batch-sizing and sequencing and timing decisions in detail. A three-phase, scenario-based solution algorithm is introduced to model demand uncertainty considering Value-at-Risk (VaR) and Conditional Value-at-Risk (CVaR) measures, while both systematic and unsystematic risk are considered. Results illustrate that the proposed modelling framework can constitute a systematic approach for the contract appraisal problem of CMOs as it can select the optimal contract mixture depending on the corresponding risk tolerance. Finally, the proposed modelling approach can constitute the basis for a computer aided tool that evaluates the feasibility and the profitability of different contract combinations.

4.2 Problem Statement

Contract Manufacturing Organizations

Pharmaceutical industry constitutes one of the most important industrial sectors, since it has an enormous impact on the quality of life of population. Furthermore, pharmaceutical industry, has a vital role in the economies of developed countries. This is also confirmed by the fact that the revenue of the worldwide pharmaceutical market at the end of 2020 reached $1.27 trillion. The necessity to transfer new medicines and vaccines to all over the world, leads to global supply chains, including primary and secondary manufacturers, warehouses, suppliers, etc. Hence, under this complex supply chain network, an ever-expanding number of multinational companies decide to outsource part of their manufacturing processes in order to reduce costs and increase their overall productivity (Jarvis, 2007). Nowadays, the pharmaceutical companies can be categorized as follows: i) R&D based multinationals, focused on the whole product life cycle (from discovery to distribution), ii) generic manufacturers, iii) biotechnology companies (mainly focused on research and drug discovery activities) and iv) Contract Manufacturing Organizations (CMOs).

Contract Manufacturing Organizations provide outsourcing services to multinational companies on a contract basis. Typically, the vast majority of CMOs is focused on secondary manufacturing when active pharmaceutical ingredients (APIs) are combined with a plethora of excipients and transformed into final products. Although CMOs don't have their own product portfolio, they play a key role in the supply chain of pharmaceutical products. Contract Manufacturing market is projected to grow at a compound annual growth rate of 9.4% and therefore to reach $188 billion by 2026, from $ 92.42 billion in 2018. (Healthcare Contract Manufacturing Outsourcing (CMO) Market - Forecasts from 2016 to 2021, 2016)

One of the main advantages of outsourcing, is that it allows large multinational companies to focus on their core competencies such as drug discovery and marketing. Furthermore, since CMOs manufacture products for multiple customers, they are benefited from economies of scale and they can decrease individual costs, regarding to the purchasing of raw material, production, and storage. Besides the above, outsourcing allows multinationals for larger product portfolio without increasing capital expenses associated with the construction of new facilities.

Main Challenges - Uncertainty

Both pharmaceutical products and processes must comply with strict guidelines, stipulated by regulatory agencies such as Food and Drug Administration (FDA) or European Medicines Agency (EMA). Thus, drug development is usually a time-consuming process. Although a drug patent usually expires 20 years after the date a company applies for it, it can take several years only for development and testing before a drug reaches the market. In particular, clinical trials alone take 2-10 years on average. As a result, pharmaceutical multinational companies typically aim to get products into the market as soon as possible to take advantage of the "market life under patent". After a patent expires, pharmaceutical products have to face strong competition from generic drugs and as a result, both value and sales typically halve.

In order to reduce their risk exposure, multinationals approach CMOs to outsource part of their manufacturing process. Since pharmaceutical products must be placed on the market as soon as possible, a contract can be often offered to a CMO even before the final approval of the regulatory agencies. However, the approval process can last more time than it is expected. Furthermore, if the new drug application is not successful, it must be revised and resubmitted. As a result, a CMO has to decide if it is a good choice to reserve part of its plant capacity to produce a set of currently developed products, whose demand window is uncertain.

In addition, even after a drug approval, the drug maker is required to perform further clinical trials (Phase IV- Post Approval Monitoring), to confirm the benefits of the drug. Often, the initial estimations of the drug effectiveness can be proven wrong or not fully accurate. Lower drug efficacy can affect the demand and the total sales. In the worst case, unexpected side-effects of a new drug can lead the regulatory agencies to decide the temporary suspension or even the withdrawal of the drug (Aronson, 2017).

Demand of currently developed drugs is affected by unsystematic risk, which is unique to each specific pharmaceutical product. In particular, four clinical trial outcomes (high success, target success, low success, failure) can be considered for these products as it is typical in the industry (Gatica et al., 2003). Although recently developed drugs are characterized by high demand uncertainty and high risk, usually they are sold at higher prices, and they are related to higher profit margins.

On the other hand, “mature” drugs, which have been already placed on the market and have been proved effective over time, are characterized by less volatile demand, since they are affected only by systematic risk. Systematic risk is inherent to the market as a whole, reflecting the impact of economic, geo-political and financial factors. At the same time, the profit margin of these products is lower since they face strong competition due to generic drugs. The demand volatility range of different types of products is also illustrated in Figure 4.1.

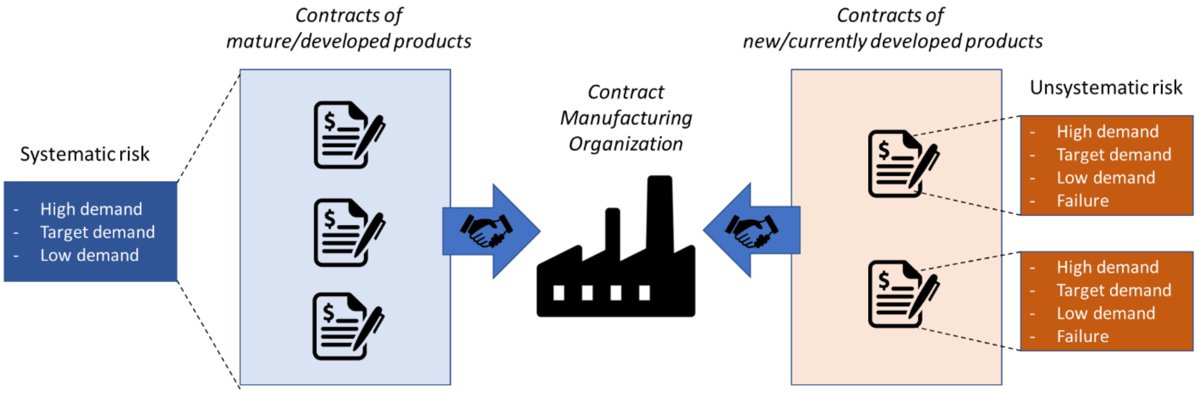

Figure 4.1 Demand uncertainty for mature and currently developed products

Under this dynamic environment, a CMO must decide the best contact combination to accept, so as to maximize the total profit while considering its tolerance to risk. When a CMO allocates its resources, the so far agreed contracts, as well as the set of available contacts, which have not been accepted yet, should be taken into consideration. The selection of the optimal contract mixture is also called as “contract appraisal problem”.

Secondary Pharmaceutical Manufacturing

Pharmaceutical production can be divided into two major subsectors. Primary manufacturing is mainly focused on the production of active pharmaceutical ingredients (APIs). On the contrary, secondary manufacturing is related to the conversion of APIs into final and suitable for usage products, such as tablets, capsules, injections etc. Typically, a secondary pharmaceutical industry operates as a multistage batch facility. In each stage, the production takes place in multiple parallel lines, The main operations that take place, usually include granulation, compression, and coating (Stefansson et al., 2011). During granulation, APIs are mixed with plethora of excipients and the mixed powder is transformed into multiparticle entities, called granules. Granulation aims to generate homogenized mixtures and contributes to cross-contamination reduction. Powder mixtures are then compressed to form final products, such as tablets. Throughout compression, key attributes such as hardness, friability, and thickness, can be monitored and controlled. Finally, the surface of intermediate products is typically covered by a thin continuous layer of solid. The main purposes of film coating are the increase of drug shelf life, the taste-masking, and the aesthetic enhancement. Coating also plays an important role in the moderation of the release profile of drug substances.

It should be mentioned that recent advances in manufacturing technology have prompted several pharmaceutical industries, to adopt continuous manufacturing (Ierapetritou et al., 2016). This movement has also been encouraged by regulatory agencies, such as FDA, to address drug shortages and recalls. However, the transition to continuous manufacturing has been proven ineffective in practice and therefore, batch operations still prevail in secondary pharmaceutical manufacturing (Marques et al., 2020).

In each production stage, multiple units operate in parallel. After each stage, production typically stops, in order to collect samples and to test the quality of products. Product-depended changeovers also occur between consecutive batches, due to required cleaning operations. Furthermore, batch integrity must be preserved. Hence, batch mixing or splitting is not allowed, in order to ensure the purity and the quality of final products (Sundaramoorthy and Maravelias, 2011). Although there are no intermediate storage units between stages, intermediate products can be stored as inventory in warehouse of the plant. Additionally, product batches can remain in a processing unit after completing their process, as long as it is required. The pharmaceutical plant operates 24 hours per day, for five days a week, to satisfy a weekly order-driven demand.

The problem can be formally stated as follows:

Given:

- A set of available and already agreed contracts with uncertain demand level
- A set of demand scenarios for each contract
- A set of processing stages with parallel processing units with limited capacity
- A time horizon
- Product-dependent changeover times
- Selling price of products
- Raw materials, operational, inventory and backorder costs
- The fixed and the batch-size dependent processing rates of products

Determine:

- The optimal contract mixture
- the detailed production plan

so as to:

- maximize the expected profit while mitigating the corresponding risk

4.3 Planning and scheduling using the Rolling Horizon framework

In this section, an hierarchical modelling framework for the integrated planning and scheduling of multistage batch pharmaceutical industries is proposed. An aggregated MILP planning model is firstly proposed considering capacity, mass balance and time horizon constraints. Planning-level decisions are made, including the determination of weekly production and inventory targets. A continuous time, general precedence, MILP scheduling model is also proposed, inspired by the work of Cerdá et al., (2020). The model focuses on the detailed scheduling of multistage batch facilities and relies on batch-sizing, unit allocation, sequencing, and timing constraints. A feedback loop is also integrated into the optimization framework so as to converge the solutions of both decision levels.

Typically, a CMO must define the best contract mixture to accept in order to maximize its profits, while considering its tolerable risk exposure. Demand uncertainty of each contract can be modelled by considering several independent scenarios. Each scenario represents a possible demand instance and is associated with a given weight, indicating the probability of its realization.

Considering multiple available contracts, and several demand scenarios, a contract selection problem is described as highly combinatorial. However, since all contract combinations and all individual scenarios are independent, the integrated planning and scheduling problem of each scenario can be solved and evaluated separately (Dimitriadis, 2000; Johnson, 2005).

Furthermore, a major challenge for a contract selection problem is typically the consideration of long-term time horizons. Hence, the solution of planning and scheduling is addressed through an hierarchical framework, based on the idea of the rolling horizon approach (Dimitriadis, 2000; Verderame and Floudas, 2008; Wu and Ierapetritou, 2007). In sections 4.3.1 and 4.3.2 the aggregated planning and the detailed scheduling models are proposed. Finally, the hierarchical framework, based on the rolling horizon approach is presented in Section 4.3.3.

4.3.1 Planning MILP model

The model constraints are presented below:

Allocation constraints

$$qw_j^{min} WV_{p,j,w} \leq Q_{p,j,w} \leq qw_j^{max} WV_{p,j,w} \quad \forall\, p \in P, j \in PJ_p, w \in W \tag{4.1}$$

Constraints (4.1) impose an upper (qw_j^{max}) and a lower (qw_j^{min}) bound on the production of each product $Q_{p,j,w}$, in production unit j, during week w.

Mass balance constraints

$$I_{p,s,w-1} + \sum_{j \in (JS_s \cap PJ_p)} Q_{p,j,w} = I_{p,s,w} + \sum_{j \in (JS_{s+1} \cap PJ_p)} Q_{p,j,w} + \\ + d_{p,s,w} - B_{p,s,w} + B_{p,s,w-1} \quad \forall\, p \in P, s \in S, w \in W \tag{4.2}$$

Constraints (4.2) express the material mass balances. In particular, the total produced and stored amount of product p from the previous week ($I_{p,s,w-1}$), must be equal to the weekly demand ($d_{p,s,w}$), the produced amount at the next production stage (s+1) and the new stored amount, $I_{p,s,w}$. If the demand cannot be fully satisfied, then that amount is denoted as backlog (or backorder), and it is represented by variable $B_{p,s,w}$. The unsatisfied demand is penalized in the objective function by considering an associated cost term. The last term of the mass balance constraints is related to the backlog of the previous week, ($B_{p,s,w-1}$). Since backorders must be satisfied as soon as possible, variable $B_{p,s,w-1}$ is added into the market demand for the current week.

$$\sum_{j\in JS_s} Q_{p,j,w} \leq \sum_{j\in JS_{s-1}} Q_{p,j,w} + I_{p,s,w-1} \quad \forall\, p\in P, s\in S, w\in W{:}\, s>1 \tag{4.3}$$

Constraints (4.3), ensure that the total production of product p at stage s, at the end of week w, should not exceed the amount that has been produced at the previous stage, plus the amount being stored from the previous week, $I_{p,s,w-1}$. Obviously, the above restriction doesn't affect the first production stage, where production is limited only by the capacity of production units.

Duration constraints

$$N_{p,j,w} \geq \frac{Q_{p,j,w}}{q_j^{max}} \quad \forall\, p\in P, j\in PJ_p, w\in W \tag{4.4}$$

The minimum number of batches for each product p, in unit j, is denoted by integer variable $N_{p,j,w}$. According to constraints (4.4), the minimum number of batches is at least equal to the quotient of the division of the produced amount $Q_{p,j,w}$, and the maximum capacity of unit j, q_j^{max}. Using an inequality constraint, if the quotient of the division leads to a non-integer number, variable $N_{p,j,w}$ is rounded up to the next higher integer.

$$T_{p,j,w} = fx_{p,j}N_{p,j,w} + \frac{Q_{p,j,w}}{vt_{p,j}} \quad \forall\, p\in P, j\in PJ_p, w\in W \tag{4.5}$$

The processing time of each product p, $T_{p,j,w}$, is given by constraints (4.5), including two terms. The first term is related to the fixed processing time, while the second is associated with the size-dependent processing time. The fixed processing time typically includes the time needed for filling and emptying the processing units, as well as the

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required time for quality control. The terms $fx_{p,j}$ and $vt_{p,j}$ express the fixed and variable processing time coefficients, respectively.

Storage constraints

$$I_{p,s,w} \leq cap_{p,s} \quad \forall\, p \in P, s \in S, w \in W \tag{4.6}$$

$$\sum_{p}\sum_{s} I_{p,s,w} \leq wc \quad \forall\, w \in W \tag{4.7}$$

Storage capacity limitations are satisfied via constraints (4.6) and (4.7). In particular, constraints (4.7) guarantee that the stored amount cannot exceed the total warehouse capacity of the plant, *wc,* while constraints (4.6), impose a capacity limitation for the stored amount of product *p,* at stage *s*, given by the parameter, $cap_{p,s}$.

Time horizon constraints

$$\sum_{p} T_{p,j,w} + \sum_{p} cl_{p,j} W\, V_{p,j,w} \leq h \quad \forall\, j \in J, w \in W \tag{4.8}$$

$$\sum_{p} \sum_{j \in (JS_s \cap PJ_p)} T_{p,j,w} \leq avl_s\, \mu_s \quad \forall\, s \in S, w \in W \tag{4.9}$$

To enhance the accuracy of the planning model, time horizon constraints (4.8) and (4.9) are also considered. According to constraints (4.8), the total processing time and the average cleaning time $cl_{p,j}$ of each production unit must be lower than the available time horizon, *h*. Additionally, constraints (4.9) state that the total production time of each production stage, must not exceed an upper limit, given by the parameter avl_s. Usually, parameter avl_s is equal to the time horizon, *h* multiplied by the number of parallel lines of stage *s*. Parameter μ_s is a sequencing factor and it has a vital role in the proposed solution framework (Verderame and Floudas, 2008; Wu and Ierapetritou, 2007). The initial value of the sequencing factor equals 1, but it can be modified during the rolling horizon algorithm. Since the planning model doesn't include timing and sequencing constraints, in some cases, the production targets provided to the scheduling level are proven infeasible. To converge the production amounts of the two models, the upper bound is adjusted to the maximum production time defined by the scheduling level. Hence, the MILP planning model is more accurate. A detailed description of the use of sequence factor is provided in section 4.3.3

Objective function

$$\max \overbrace{\sum_{c} in_c}^{initial\ contarct\ payment} + \overbrace{\sum_{s}\sum_{w}\sum_{p}\sum_{j\in(JS_s\cap PJ_p)} W_{p,j,w}\, d_{p,s,w} pr_p}^{total\ sales} - \overbrace{\sum_{w}\sum_{p} B_{p,3,w} bc_p}^{backlog\ cost} - \overbrace{\sum_{w}\sum_{p}\sum_{s} I_{p,s,w}\, ic_p}^{inventory\ cost} - \overbrace{\sum_{w}\sum_{p}\sum_{j\in PJ_p} Q_{p,j,w}\, qc_p}^{production\ cost} - \overbrace{\sum_{p} fr_p rc_p}^{raw\ material\ fixed\ cost} - \overbrace{\sum_{p} rc_p(\sum_{j\in PJ_p}\sum_{w}(Q_{p,j,w}) - fr_p)}^{raw\ material\ variable\ cost} \quad (4.10)$$

The objective function aims at maximizing the total profit. The main income of the company is related to the initial payment of each signed contract (in_c), and the total revenue of sales. On the other hand, expenses include backlog, inventory, production, and raw material costs. It is assumed that if a contract is signed, a minimum amount of raw materials must be purchased regardless of the actual demand and the final production level. Thus, a term related to the fixed cost of raw materials is considered as well.

4.3.2 Scheduling MILP model

In this section, a general precedence-based MILP is proposed, inspired by the work of Cerdá et al., (2020). The model is focused on the scheduling of multistage, multiproduct batch processes, typically met in secondary pharmaceutical industries. A description of model sets, variables and parameters is presented below, while constraints are categorized based on the type of decision (e.g. allocation, batch sizing, timing, sequencing, etc.).

Allocation constraints

$$\sum_{p \in P} YP_{b,p} \leq 1 \;\; \forall \, b \in B \tag{4.11}$$

$$\sum_{j \in (JS_s \cap PJ_p)} YU_{b,p,j} \leq YP_{b,p} \;\; \forall \, b \in B, p \in P, s \in S \tag{4.12}$$

Constraints (4.11) ensure that any batch is assigned to at most one product *p*. Furthermore, as it is stated by constraints (4.12), each batch *b* is allocated to at most one processing unit *j*, in each production stage *s*.

Mass balance constraints

$$ininv_{p,s} + \sum_{b \in B} QB_{b,p,s} = dm_{p,s} - BA_{p,s} + INV_{p,s} \;\; + \sum_{b \in B} QB_{b,p,s+1} \;\; \forall \; p \in P, s \in S \tag{4.13}$$

Mass balances are expressed for each product *p* and production stage *s*, using constraints (4.13). In particular, the initial inventory, $ininv_{p,s}$, plus the total production of product batches, must be equal to the customer's demand, $dm_{p,s}$, the amount processed in the next production stage *s*+1 and the new stored amount $INV_{p,s}$. If demand cannot be fully satisfied, it is backlogged by utilizing variable $BA_{p,s}$.

Timing constraints

$$TP_{b,s} = \sum_{p} \sum_{j \in (JS_s \cap PJ_p)} YU_{b,p,j} fx_{p,j} + \frac{QBV_{b,p,j}}{vt_{p,j}} \quad \forall \, b \in B, s \in S \tag{4.14}$$

The processing time of batch b of product p, $TP_{b,s}$, is expressed by constraints (4.14). Similarly to constraints (4.5), the processing time has two contributions. The first term is associated with the fixed processing time, whereas the second one with the size-dependent processing time. Variable, $QBV_{b,p,j}$ represents the variable component of batch size.

$$CT_{b,s} = ST_{b,s} + TP_{b,s} + WT_{b,s} \quad \forall\, b \in B, s \in S \tag{4.15}$$

According to constraints (4.15) the completion time of batch b, $CT_{b,s}$, must be equal to the sum of the corresponding starting time, $ST_{b,s}$ and the processing time, $TP_{b,s}$. In some cases, a waiting time is allowed between sequential stages. The waiting time of batch b in stage s, is represented by variable $WT_{b,s}$. In case of zero-wait storage policy, variable $WT_{b,s}$ is set to zero.

$$CT_{b,s} + ch_{p,p'} \leq ST_{b',s} + h(2 - YU_{b,p,j} - YU_{b',p',j}) + h(1 - XB_{b,b',j})$$
$$\forall\, b \in B, b' \in B, p \in P, p' \in P, s \in S, j \in (JS_s \cap PJ_p): p' \neq p, b' > b \tag{4.16}$$

$$CT_{b',s} + ch_{p',p} \leq ST_{b,s} + h(2 - YU_{b,p,j} - YU_{b',p',j}) + hXB_{b,b',j}$$
$$\forall\, b \in B, b' \in B, p \in P, p' \in P, s \in S, j \in (JS_s \cap PJ_p): p' \neq p, b' > b \tag{4.17}$$

Constraints (4.16) and (4.17) define the relative sequencing of batches at each processing unit j (Kopanos et al., 2010a). Since batch b' is processed after batch b, in unit j of stage s, ($XB_{b,b',j} = 1$), the starting time, $ST_{b',s}$, must be greater than the sum of the completion time $CT_{b,s}$ and the corresponding changeover time $ch_{p,p'}$. On the other hand, if the general precedence variable is equal to 0, constraints (4.17) force variable $ST_{b,s}$ to be greater than the sum of variables $CT_{b',s}$ and $ch_{p,p'}$. If batches b and b' are not processed in the same unit j, ($YU_{b,p,j} = YU_{b',p',j} = 0$), constraints (4.16) and (4.17) are relaxed.

$$CT_{b,s} \leq CT_{b',s} + h(2 - YU_{b,p,j} - YU_{b',p,j})$$
$$\forall\, b \in B, b' \in B, p \in P, s \in S, j \in (JS_s \cap PJ_p): b' > b, s = |S| \tag{4.18}$$

To avoid symmetric solutions, the processing of batches that contain the same product *p* can be preordered. According to constraints (4.18), batches assigned to the same product *p* and the same unit *j*, must be processed in the same order as they appear in set *B*. Constraints (4.18) is applied only to the last production stage since otherwise, a subset of feasible solutions could not be detected in the solution search space (Cerdá et al., 2020).

$$ST_{b,s+1} = CT_{b,s} + trs_p \sum_{p} QB_{b,p,s} \quad \forall\, b \in B, s \in S{:}\, s < |S| \tag{4.19}$$

Constraints (4.19) determine the timing of batches between consecutive stages. The starting time of batch *b*, in stage *s*+1, must be equal to its completion time in the previous stage *s,* plus the necessary transferring time, which is given by the parameter trs_p.

$$CT_{b,s} \leq h \sum_{p} \sum_{j \in (JS_s \cap PJ_p)} YU_{b,p,j} \quad \forall\, b \in B, s \in S \tag{4.20}$$

$$ST_{b,s} \leq h \sum_{p} \sum_{j \in (JS_s \cap PJ_p)} YU_{b,p,j} \quad \forall\, b \in B, s \in S \tag{4.21}$$

$$WT_{b,s} \leq h \sum_{p} \sum_{j \in (JS_s \cap PJ_p)} YU_{b,p,j} \quad \forall\, b \in B, s \in S \tag{4.22}$$

Constraints (4.20)-(4.22), guarantee that variables $CT_{b,s}$, $ST_{b,s}$ and $WT_{b,s}$ are forced to zero if batch *b* is not allocated to any product *p*, or any unit *j* at stage *s*.

Batch sizing constraints

$$QB_{b,p,s} = \sum_{j \in JS_s} (YU_{b,p,j}\, q_j^{min} + QBV_{b,p,j}) \quad \forall\, b \in B, p \in P, s \in S \tag{4.23}$$

$$QBV_{b,p,j} \leq (q_j^{max} - q_j^{min}) YU_{b,p,j} \quad \forall\, b \in B, p \in P, s \in S, j \in (JS_s \cap PJ_p) \tag{4.24}$$

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The size of batch *b,* which consists of two individual terms, is defined by constraints (4.23). The fixed component is equal to the minimum capacity of the corresponding processing unit, q_j^{min}. On the other hand, the variable batch size is expressed by variable $QBV_{b,p,j}$. Furthermore, as it stated by constraint (4.24), the variable batch size must not exceed the maximum capacity q_j^{max}, minus the minimum capacity of processing unit *j.*

$$\sum_{j\in(JS_s \cap PJ_p)} YU_{b,p,j} = \sum_{j\in(JS_{s-1} \cap PJ_p)} (YU_{b,p,j}) + YII_{b,p,s-1} \qquad (4.25)$$
$$\forall\, b \in B, p \in P, s \in S : s > 1$$

Additionally, a batch *b*, in stage *s*, can be either produced by a processing unit *j* or it can be fulfilled by the inventory being stored in the warehouse. To take this issue into account, an auxiliary binary variable $YII_{b,p,s}$ is introduced, which is equal to 1 only if batch *b* in stage *s* is covered by stored amount. Constraints (4.25) ensure that a batch *b* can be allocated to unit *j* in stage *s*, only if it has been previously produced or it has been covered by the stored amount in previous stage, *s*-1.

$$QB_{b,p,s} \le UINV_{b,p,s-1} + QB_{b,p,s-1} \qquad \forall\, b \in B, p \in P, s \in S : s > 1 \qquad (4.26)$$

$$UINV_{b,p,s} \le YII_{b,p,s}ininv_{p,s} \quad \forall\, b \in B, p \in P, s \in S \qquad (4.27)$$

$$\sum_{b\in B} UINV_{b,p,s} \le ininv_{p,s} \quad \forall\, p \in P, s \in S \qquad (4.28)$$

Furthermore, variables $UINV_{b,p,s}$ are introduced, to express the stored amount of product *p*, that is being used to fulfil batch *b,* in stage *s*. According to constraints (4.26), the batch size of batch *b* in stage *s*, should be less than the produced amount of the previous stage, $QB_{b,p,s-1}$, and the amount received by the warehouse, $UINV_{b,p,s-1}$. Constraints (4.27), ensure that the stored amount of product *p* in stage *s*, used for satisfying batch *b*, does not exceed the total inventory of product *p*, $ininv_{p,s}$. Finally, constraints (4.28) guarantee that the total used inventory, cannot exceed the initially stored amount of product *p* at stage *s*.

Storage constraints

$$INV_{p,s} \leq cap_{p,s} \;\; \forall \; p \in P, s \in S \tag{4.29}$$

$$\sum_{p}\sum_{s} INV_{p,s} \leq wc \tag{4.30}$$

Similar to constraints (4.6) and (4.7), constraints (4.29) and (4.30) ensure that the net amount of storage material does not exceed the storage capacity of the plant. In particular, constraints (4.29) determine the storage capacity for each individual product at each stage s, while the warehouse capacity limitations are imposed by constraints (4.30).

Underproduction constraints

$$\sum_{b \in B} QB_{b,p,s} + PU_{p,s} \geq tprod_{p,s} \quad \forall \; p \in P, s \in S \tag{4.31}$$

$$INV_{p,s} + IU_{p,s} \leq tinv_{p,s} \quad \forall \; p \in P, s \in S \tag{4.32}$$

The decisions made by the proposed MILP planning model define the production targets for the scheduling level. However, the capacity of the plant could be overestimated by the planning model, and thus the production targets would be proven infeasible. Hence, we introduce two slack variables $PU_{p,s}$ and $IU_{p,s}$, expressing the total underproduction and inventory underproduction of product p in stage s, respectively. Constraints (4.31) and (4.32) are included to allow for potential violation of the production targets and maintain the robustness of the model. Additionally, both slack variables are penalized in the objective function. It should be noted that both constraints (4.31) and (4.32) can be written as equalities. However, the usage of inequality constraints can potentially improve the CPU time without affecting the quality of the solution.

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Objective function

$$max \overbrace{\sum_{p} pr_p dm_{p,3}}^{total\ sales} - \overbrace{\sum_{p} bc_p BA_{p,3}}^{backlog\ cost} - \overbrace{\sum_{p}\sum_{s} ic_p INV_{p,s}}^{inventory\ cost}$$
$$\overbrace{\sum_{b}\sum_{p}\sum_{s} qc_p QB_{b,p,s}}^{production\ cost} - \overbrace{puc \sum_{s}\sum_{p} PU_{p,s}}^{underproduction\ cost} - \overbrace{iuc \sum_{s}\sum_{p} IU_{p,s}}^{inventory\ underproduction\ costt} \tag{4.33}$$

In accordance with the objective of the planning model, the maximization of total profit is considered as the main target of the scheduling model. The objective function takes into account the various individual costs, such as backlog, inventory and production cost, along with the total sales of final products. The two final terms aim to minimize the slack variables related to the total underproduction, and inventory underproduction.

4.3.3 Rolling horizon framework

Among the different decision levels, tactical planning and medium-term scheduling are strongly connected. One of the main challenges in the integration of production planning and scheduling is the development of computationally effective formulations for complex production facilities, which include multiple product routes, and sequence-dependent changeovers. The major modelling approaches for the integration of planning and scheduling decisions are presented in detail by Maravelias and Sung, (2009). Furthermore, modern process industries must satisfy multiple customer orders, considering frequent demand fluctuations. Hence, processing equipment has to be fully utilized, while at the same time, production targets must be feasible (Georgiadis et al., 2019a).

To address this challenge, the integrated planning and scheduling problem can be solved via an hierarchical framework, based on a rolling horizon approach. The main idea of the rolling horizon algorithm is the division of the initial long-term time horizon, *h,* into a sequence of *N* smaller subperiods, (i.e., weeks). Each subperiod can be optimized in an iterative way. Two new subsets, T_s and T_p are also introduced, to represent the scheduling and the planning time-blocks, respectively. In each iteration, only decisions related to the scheduling time block, T_s, are made in detail, while the rest subperiods are considered in an aggregate manner. Typically, in process industries the scheduling horizon is equal to one week, but this could vary depending on the specific problem features.

In the first iteration of the rolling horizon algorithm, the planning time-block consists of the overall planning horizon ($T_p = \{n_1, .. n_N\}$), while subset T_s includes only the first time period ($T_s = \{n_1\}$). Hence, the aggregated planning model is solved, considering the entire planning horizon T_p, and the solution determines production targets for each subperiod. Then, the medium-term scheduling model is solved for solely the first subperiod and detailed decisions are made.

In the second iteration, the subset T_s is updated so that $T_s = \{n_2\}$, while $T_p = \{n_1, .. n_N\}$. Hence, the aggregated planning model is solved again for the entire planning horizon, h. However, decisions related to the first subperiod are considered fixed, since they have already been taken by the scheduling model in the first iteration. Considering the updated production targets, the scheduling model is solved for the second subperiod, $T_s = \{n_2\}$, and the related scheduling decisions are also fixed.

The procedure described above, is repeated until all subperiods are solved in detail by the medium-term scheduling model. Production targets can be revised in each iteration. A brief schematic representation of the rolling horizon framework is illustrated in Figure 4.2.

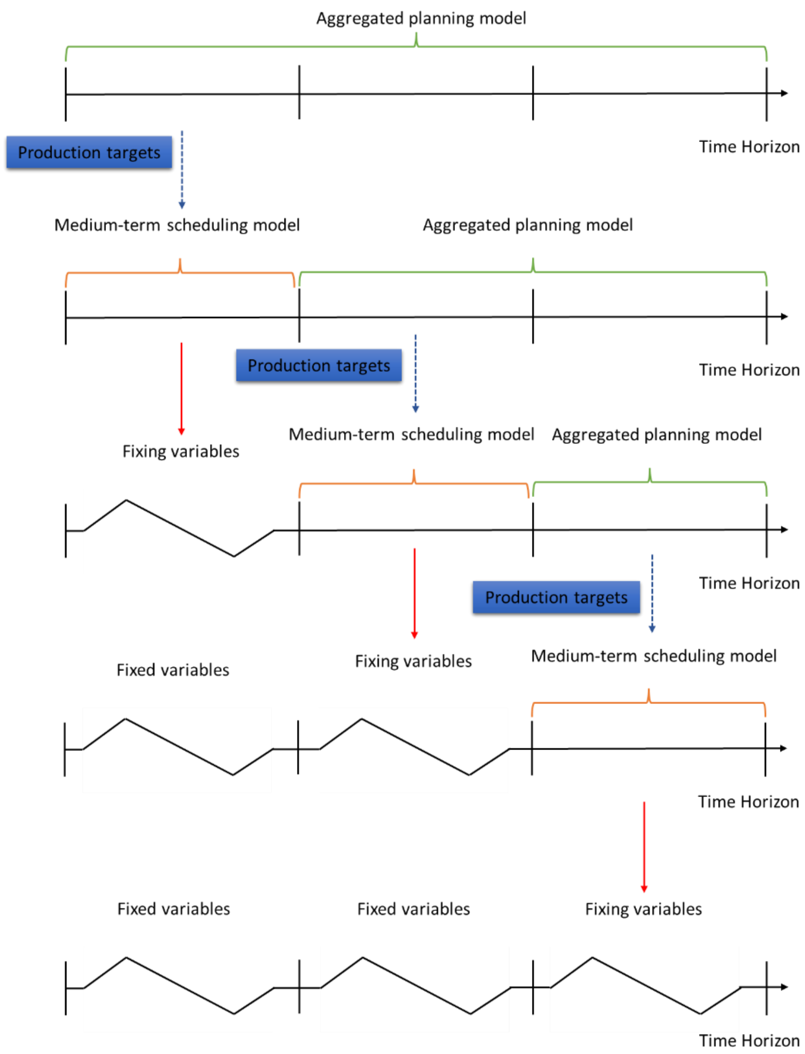

Figure 4.2 Rolling horizon framework

One of the main drawbacks of the rolling horizon framework is that the production capacity of the plant cannot be represented so accurately by the aggregated planning model (Li and Ierapetritou, 2010). Thus, the defined production targets may be often proven suboptimal or even infeasible by the scheduling model. To address this issue, the rolling horizon framework should allow for feedback between scheduling and planning models. This can be achieved by including additional feasibility constraints into the planning model, in order to reduce the feasible solution space and impose accurate enough capacity upper bounds (Verderame and Floudas, 2008; Wu and Ierapetritou, 2007). In particular, time horizon constraints (4.9) are included in the proposed planning model. To allow for feedback between the two optimization levels, a sequence factor μ_s is also introduced (Wu and Ierapetritou, 2007). The sequence factor has a significant role in the rolling horizon algorithm, as it represents the impact of sequencing constraints in the planning model. Thus, an accurate value of the sequence factor can lead to convergence between planning and scheduling solutions. The initial value of the sequence factor equals 1. However, if there is a gap between planning and scheduling production levels, the sequence factor is updated for the subsequent iterations as follows:

$$\mu_s^{iter} = \mu_s^{iter-1} \frac{P_s^{scheduled}}{P_s^{planned}} \quad \forall\ s \in S \tag{4.34}$$

Parameters $P_s^{planned}$ and $P_s^{scheduled}$, denote the total production targets for production stage *s*, as defined by the planning and the scheduling optimization levels, respectively. Apparently, the sequence factor cannot exceed the value of 1, as in that case, the time horizon constraints would be relaxed and deactivated. If the plant capacity is overestimated by the planning model, the production targets may be proven infeasible by the scheduling model ($P_s^{planned} > P_s^{scheduled}$). In this case the sequencing factor will be adjusted to a smaller value, for the following iterations of the algorithm. Rarely, the plant capacity can be even underestimated by the planning model, and therefore the sequence factor is forced to an increased value. It should be noted that if there is a gap between planning and scheduling production levels, an iterative procedure could be applied in order to obtain the optimal value of the sequencing factor. However, this is not a major target, as parameter μ_s can be modified at each iteration (Verderame and Floudas, 2008; Wu and Ierapetritou, 2007).

4.4 Solution framework

In this section, a systematic approach for the contract appraisal problem is proposed, aiming to determine decisions on which contract to accept, while considering resource allocation and demand uncertainty. In particular, given a set of available and already agreed contracts, a CMO must define the best contract mixture to maximize its profits, while considering the corresponding risk exposure. However, the consideration of multiple contracts and several demand scenarios for each individual contract, renders the contract selection problem a complex task. The development of a two-stage stochastic model for the strategic planning of CMOs could be proven inaccurate, as sequencing decisions cannot be considered in detail by an aggregated planning model. Additionally, the examination of long-term time horizons also imposes limitations on developing tractable integrated planning and scheduling MILP formulations. To address this issue, a solution framework is proposed.

Typically an MILP model can be written in the following form:

$$\begin{gathered} \max a^T x + b^T y \\ s.t. \\ Ax + By \leq c \\ x^L \leq x \leq x^U \\ x \in \mathbb{R}^n \\ y \in \{0,1\} \end{gathered} \tag{4.35}$$

Dimitriadis (2000), shows that if variable vectors x and y can be partitioned into p independent vectors, the problem (4.35) is decomposable. Furthermore, each individual P-MILPs can be solved in parallel to reduce the required computational time.

It should be noted that in the contract appraisal problem, all contract combinations, as well as all scenarios, are independent. Thus, instead of considering all contracts and scenarios as part of a single MILP model, each one of them can be evaluated independently (Dimitriadis, 2000; Johnson, 2005). In particular, the proposed rolling horizon framework for the integrated planning and scheduling can be solved for each individual contract combination and each combined scenario. Afterwards, the generated solutions can be utilized to construct the profit distribution of each combination of contracts. To address large problem instances that involve numerous scenarios, an MILP-based scenario reduction framework can also be employed (Li and Floudas, 2014). The proposed solution framework consists of three phases, which are thoroughly described below. A schematic representation of the proposed solution strategy is also illustrated in Figure 4.3.

1st phase

The first phase is focused on the assessment of the feasibility of each contract combination. In particular, the predominant scenario of each combination is considered by solving the aggregated planning MILP model. If the generated solution leads to full demand satisfaction, the underlying contract combination is defined as feasible. On the contrary, if a contract combination is proven infeasible, then any combination that is a superset of the former must also be infeasible. For example, if the combination of contracts C1 and C2 is infeasible then the combination with the contracts C1, C2 and C3 is also infeasible.

2nd phase

According to the second phase, the predominant scenario of each combination that has been proven feasible in the first phase is solved, using the integrating planning and scheduling MILP framework. If any iteration of the rolling horizon framework results in partial demand satisfaction (backlog generation), the contract combination is deemed infeasible. Furthermore, any combination that is a superset of the former is also deemed infeasible.

3rd phase

Regarding the third phase of the proposed algorithm, the planning and scheduling problem of each combination is solved for each combined scenario, by applying the rolling horizon algorithm. Considering scheduling level decisions, the total profit can be accurately estimated for all scenarios of a contract combination and thus, the corresponding profit distribution can be constructed. Depending on their tolerance to risk, decision-makers can choose the optimal contract combinations that maximize the total profit.

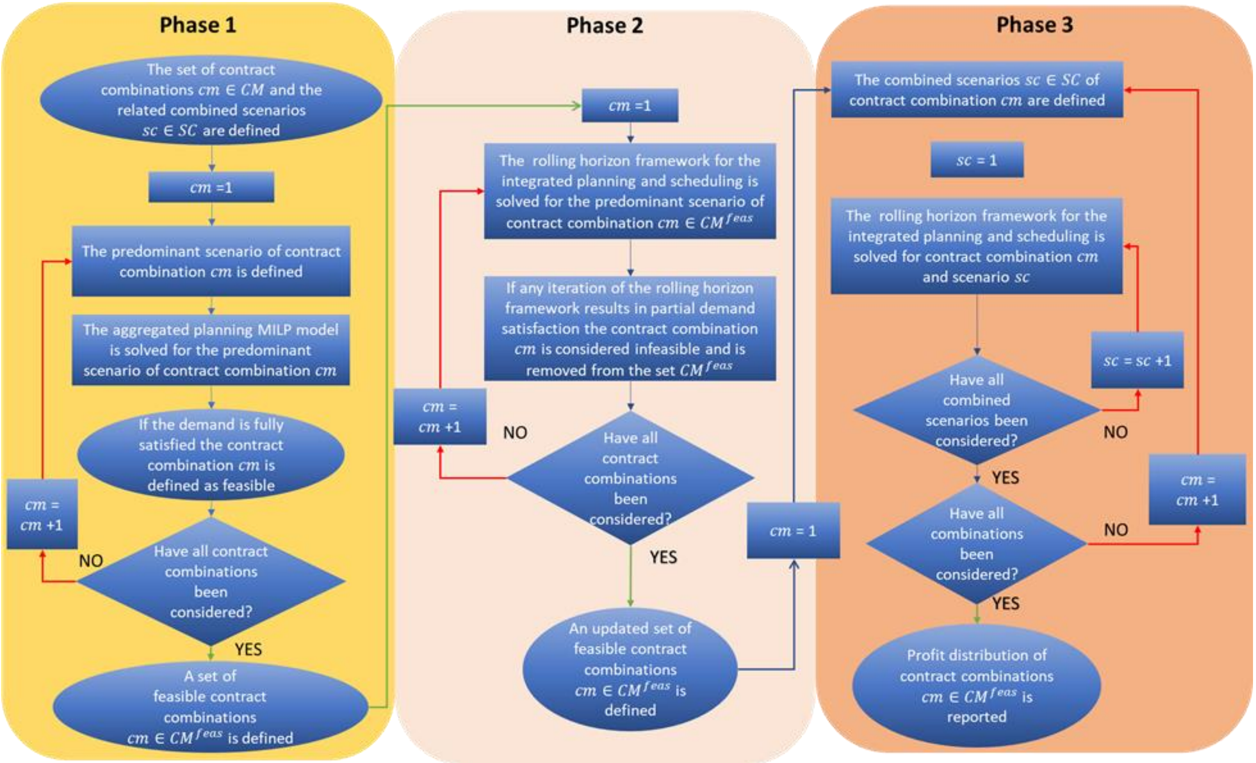

Figure 4.3 Schematic representation of the solution strategy.

Assessment of Risk

Nowadays, process industries try to manage various types of risk. Although most industries try to avoid risks, sometimes a judicious exposure to risk can create a competitive advantage for a company. Risk can be defined as the volatility of unexpected outcomes, which can represent the value of assets, costs, or profits. Understanding and measuring risk means that decision-makers can consciously plan for the consequences of adverse outcomes. Typically, risk associated with process industries can be defined as the probability of not meeting a specific profit or cost target. Various risk measures can be used to assess the risk, such as variance, variability index, downside risk, Value-At-Risk (VaR) and Conditional Value-At-Risk (CVaR), (Vieira et al., 2020). In the proposed solution framework, both VaR and CVaR are used to evaluate the corresponding risk of each contract combination.

Value-at-Risk is a widely used risk measure, which was firstly introduced by the financial institution J. P. Morgan (Jorion, 2000). Given a profit distribution and a specified confidence level (α), Value-at-Risk represents the maximum profit between the α% worst profit realizations. A more general definition of VaR is given by the profit value corresponding to the 1-α-quantile. For a specific profit distribution P, VaR can be defined as:

$$VaR_a(P) = F_P^{-1}(1-\alpha) = Q_P(1-a) \tag{4.36}$$

where, $F_P^{-1}(1-\alpha)$ is the inverse cumulative distribution function that is equal to the quantile function, $Q(1-a)$. Although VaR can provide a good approximation of the corresponding risk it suffers from a major drawback. In particular, VaR cannot capture the profit levels associated with the extreme data points and the tail of the probability distribution. Therefore, decision-makers have no indication regarding the profit distribution beyond the confidence level α.

To face this issue, alternative risk measures, such as Conditional-Value-at-Risk, have been also introduced. Conditional-Value-at-Risk, which is also called Expected shortfall or Average Value-at-Risk, is a risk measure that is mainly used in the field of financial risk measurement. For a given profit distribution P, CVaR represents the average of all profit levels that are worse than the VAR, at a given level of confidence, α:

$$CVaR_a(P) = \frac{1}{\alpha}\int_1^a VaR_c(P)\,dc \tag{4.37}$$

For example, the $CVaR_{95\%}$ is calculated by taking the average of profit levels in the worst 5% of cases. A graphical representation of VaR and CVaR measures for a confidence level, α=90%, is shown in Figure 4.4.

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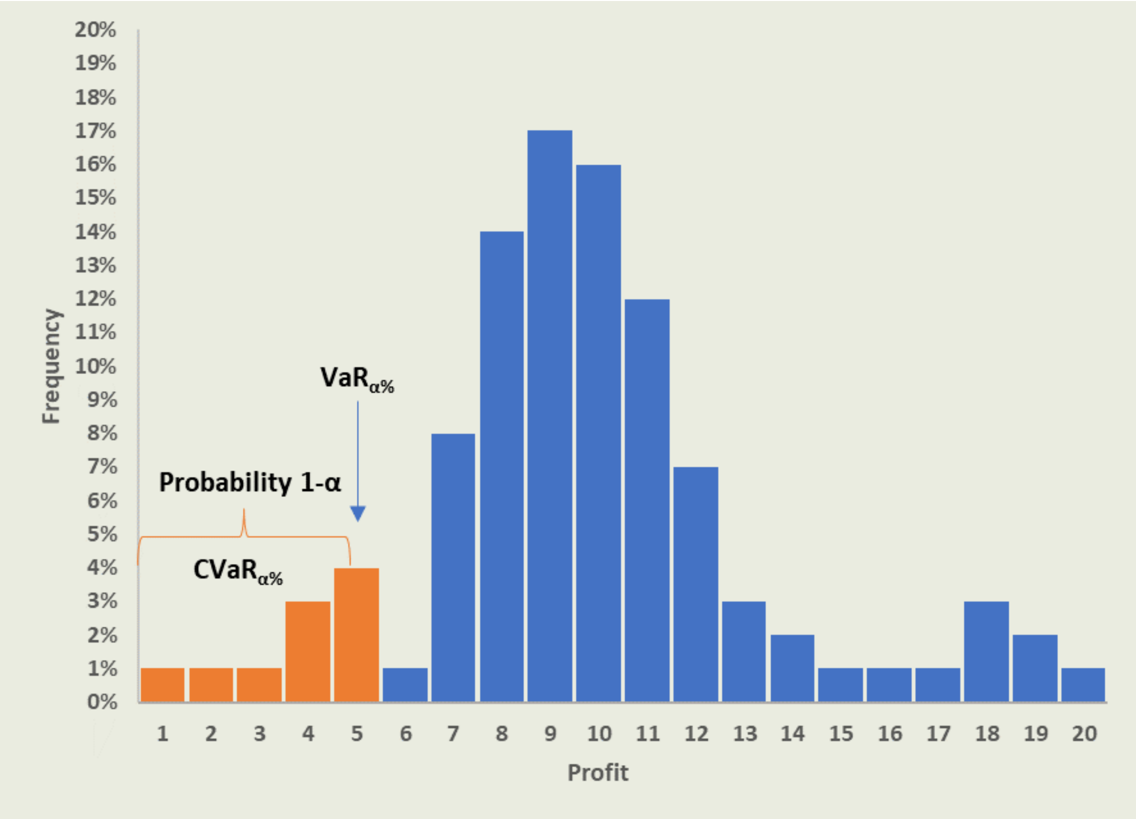

Figure 4.4 Graphical representation of VaR and CVaR measures for a confidence level α=90% and a profit distribution P

Scenario reduction model

Making accurate decisions usually requires the consideration of numerous scenarios. Considering combinations of multiple contracts, the rolling horizon framework must be solved several times according to the proposed solution framework. To cope with this challenge, a scenario reduction framework proposed by Li and Floudas, (2014), can be applied. Considering an initial demand distribution of a contract combination, the scenario reduction model can define a new distribution by removing a user-defined number of scenarios. The scenario reduction is mainly achieved by minimizing the probabilistic distance between the initial and the reduced distribution of uncertain parameters. The probability of each removed scenario is added to the initial probability of the remaining scenario that is closest to it.

A notable advantage of this framework is that except from the input parameter distribution, the output distribution is also considered. For instance, considering a contract selection problem, both demand and expected profit distributions can be taken into account and thus, more accurate solutions can be obtained.

A detailed description of the sets, variables and constraints of the scenario reduction MILP-based model is given in Appendix C.1. To apply the scenario model to the contract selection problem, a set of input data must be first defined to compute the distance between any two scenarios s and s', of a contract combination. In particular, the distance parameter $c_{s,s'}$ can be calculated as follows:

$$c_{s,s'} = \sum_{p} \sum_{w} \left| d_{p,s,w} - d_{p,s',w} \right| + |f_s^* - f_{s'}^*| \tag{4.38}$$

,where the parameter $d_{p,s,w}$ express the demand of product p in week w and scenario s, and the parameter f_s^* represents the expected profit of scenario s. However, obtaining the optimal objective value for each scenario of the initial distribution by solving the proposed rolling horizon framework, would not be an efficient approach, as it is a time-consuming process. Furthermore, having already obtained the optimal solution of all scenarios for a combination of contracts, the solution of the scenario reduction model would be useless, as in this case, the profit distribution could be easily constructed. To overcome this limitation, the initial profit distribution can be efficiently approximated by solving the proposed aggregated planning MILP model for each individual scenario. Even when a large number of scenarios is considered, the proposed planning model can be easily solved for each scenario and thus, a good profit estimation can be obtained in a short amount of time.

To summarize, the following preliminary computations must be made, in order to apply the scenario reduction MILP model:

1) Obtain the optimal objective value for each scenario of the initial discrete distribution by solving the proposed aggregated planning MILP model
2) Compute the maximum, minimum and expected objective value of all scenarios of the initial discrete distribution

3) Compute the distance between any two scenarios s and s' as described by equation (4.38)

4.5 Application studies

The efficiency and the applicability of the proposed framework is illustrated considering two representative case studies. Both problems focus on a multi-stage batch facility of the secondary pharmaceutical industry, consisting of three individual processing stages (granulation, compression, and coating). Each stage includes multiple production units with varying capacity and production rates. The time horizon is equal to 1 year (or 52 weeks), and a weekly demand must be fulfilled for each product.

To model demand uncertainty, four demand scenarios are defined for each contract (high, target and low demand, and failure), as it is typical in the pharmaceutical industry (Gatica et al., 2003; Marques et al., 2020; Shah, 2004). Usually, demand of mature products which have been already placed on the market is stable, and it is subject only to systematic risk. Hence, combinations of contracts with already developed products consist of the same demand scenarios, including high, target and low demand with the same realization probabilities. This is a strong assumption as the demand of these products is mainly affected by major socio-economic or geopolitical issues, such as a pandemic or a financial crisis. On the other hand, demand of currently developed drugs is usually more volatile, since unexpected side-effects can cause a significant demand reduction or even the withdrawal of the drug. Hence, if a combination includes contracts with new drugs, the probability of combined scenarios is calculated as the product of the probabilities of the new drugs and the probability of the developed products.

An illustrative example is firstly presented, considering a medium-sized problem instance. In section 4.5.2, a realistic large-scale problem is solved, while the capacity expansion, by installing an additional processing unit in the last processing stage, is examined in section 4.5.3. The CMO must decide the best contract combination among a set of available and already agreed contracts in order to maximize its profit and mitigate the risk.

4.5.1 Illustrative example

In the first problem instance, the CMO must decide the best contract combination among 6 contracts. Contact C1 is already agreed. Contracts C1-C3 consist of mature products with smaller demand fluctuations and lower selling prices, while contracts C4-C6 include currently developed drugs with higher selling prices. Demand scenarios of each contract are given in Table 4.2. Furthermore, all data related to the illustrative example are presented in detail in Tables C1–C15 in the Appendix C.2.

The total number of combinations can be calculated as follows:

$$2^{contracts} - max\left(1, \sum_{c=1}^{agreed\ contracts} 2^{Contracts-c}\right) \tag{4.39}$$

Since contract C1 is already agreed, the 6 contracts lead to 31 combinations (2^6–2^5). Contract combinations that include only contracts C1-C3 are subject only to systematic risk and thus, consist only of 3 scenarios (high, target and low demand). On the contrary, the scenario probability of combinations that include contracts with new drugs (e.g., C4-C6), is calculated as the product of the probabilities of the new drugs and the probability of the developed products. For example, the contract combination C1-C2-C6 consists of 12 (or 3·4) individual scenarios which are presented in detail in Table 4.1.

Table 4.1 Demand scenarios of contract combination C1-C2-C6

Probability	2,5%	20,0%	2,5%	4,0%	32,0%	4,0%
C1	High	Target	Low	High	Target	Low
C2	High	Target	Low	High	Target	Low
C6	High	Target	Target	Target	Target	Target
Probability	12,0%	3,5%	16,0%	3,5%	2,5%	20,0%
C1	High	Target	Low	High	Target	Low
C2	High	Target	Low	High	Target	Low
C6	Low	Low	Low	Fail	Fail	Fail

`

To solve this problem, the proposed solution algorithm is utilized. According to the first phase of the solution algorithm, all combinations are solved using the aggregated planning model for the corresponding predominant scenario (target demand). The underlying contract combination is defined as feasible if the solution leads to full demand satisfaction. On the other hand, if the solution leads to backlog, then the contract combination is regarded as infeasible and any combination that is a superset of the former must also be infeasible

In the second phase of the algorithm the set of feasible combinations are solved for their predominant scenario by using the proposed integrated planning and scheduling rolling horizon framework. Similarly to phase 1, if the obtained solution leads to backlog, then the contract combination and any superset of the former are considered infeasible. In particular, both contract combinations C1-C3-C4 and C1-C4-C5 were proven feasible in the first, but not in the second stage of the algorithm.

Table 4.2 Contract data

contracts	**Contract availability / Product type**	**Products**	**Demand multiplier for each scenario and probability of realization**			
			High	Target	Low	Fail
C1	Agreed/developed	1,2	1.2 (10%)	1 (80%)	0.8 (10%)	0 (0%)
C2	non agreed/developed	3,4	1.2 (10%)	1 (80%)	0.8 (10%)	0 (0%)
C3	non agreed/developed	5,6,7	1.2 (10%)	1 (80%)	0.8 (10%)	0 (0%)
C4	non agreed/developed	8,9,10	1.2 (15%)	1 (60%)	0.5 (20%)	0 (5%)
C5	non agreed/developed	11,12	1.4 (20%)	1 (50%)	0.4 (20%)	0 (10%)
C6	non agreed/developed	13,14	1.7 (25%)	1 (40%)	0.2 (15%)	0 (20%)

Finally, the integrated planning and scheduling rolling horizon framework is solved, for all scenarios of each feasible contract combination. In this phase, the scenario reduction MILP model is used to reduce computational time by considering up to 10 scenarios for each combination. The solution CPU time for each scenario ranges from 10 to 15 minutes, depending on the complexity of the problem.

The expected profit, the Value-at-Risk, the Conditional Value-at-Risk, and the maximum profit for each feasible contract combination are presented in Table 4.3.

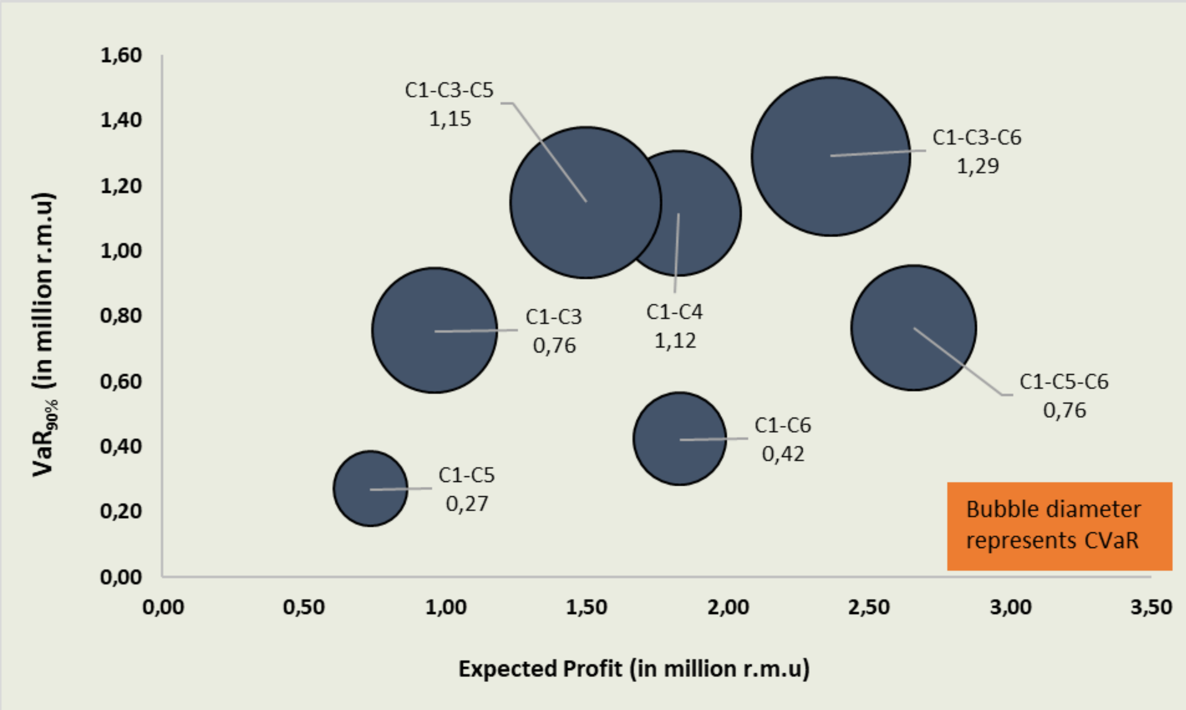

Figure 4.5 Expected profit, $VaR_{90\%}$ and $CVaR_{90\%}$ of each contract combination

Table 4.3 Summary of results

Feasible Contract combination	Exp. Profit	$VaR_{90\%}$	$VaR_{95\%}$	$CVaR_{90\%}$	$CVaR_{95\%}$	Max. Profit
C1-C3	0.96	0.76	0.76	0.76	0.76	1.15
C1-C4	1.83	1.12	0.43	0.76	0.42	2.46
C1-C5	0.74	0.27	0.27	0.27	0.27	1.09
C1-C6	1.83	0.42	0.42	0.42	0.41	3.42
C1-C3-C5	1.50	1.15	1.15	1.10	1.06	1.99
C1-C3-C6	2.36	1.29	1.29	1.22	1.16	4.30
C1-C5-C6	2.66	0.76	0.76	0.76	0.76	4.23

**The values represent millions of relative monetary units (r.m.u.)*

A bubble chart of the expected profit, the $VaR_{90\%}$ and the $CVaR_{90\%}$ is also illustrated in Figure 4.5. In particular, the diameter of each bubble represents the $CVaR_{90\%}$ of contract combinations. A large bubble in the top right-hand corner of the diagram represents a good contract combination, implying high expected profit, $VaR_{90\%}$ and $CVaR_{90\%}$ values.

Following a risk-neutral approach, the combination C1-C5-C6 seems to be the optimal one, as it leads to the maximum expected profit. However, the combination C1-C3-C6 is a more attractive option, when a risk-averse policy is applied. Considering the $VaR_{90\%}$, in this case the total profit will surpass the 1.29 million of relative monetary units (r.m.u), with a 90% confidence interval. Furthermore, the mean of the worst 10% of scenarios will be equal to 1.16 million. Finally, it should be noted that the contract combination C1-C6 constitutes a sub-optimal choice, as the combination C1-C4 leads to the same expected profit value with lower risk exposure.

4.5.2 Large problem instance

This problem includes 12 contracts, with contract C1 already signed. The independent demand scenarios of each contract are summarized in Table 4.4. The production facility consists of 3 batch stages, while 2 processing units operate in parallel in each stage (processing units 1-6). All data related to the problem under study are presented in Tables C16-C31 in Appendix C.3.

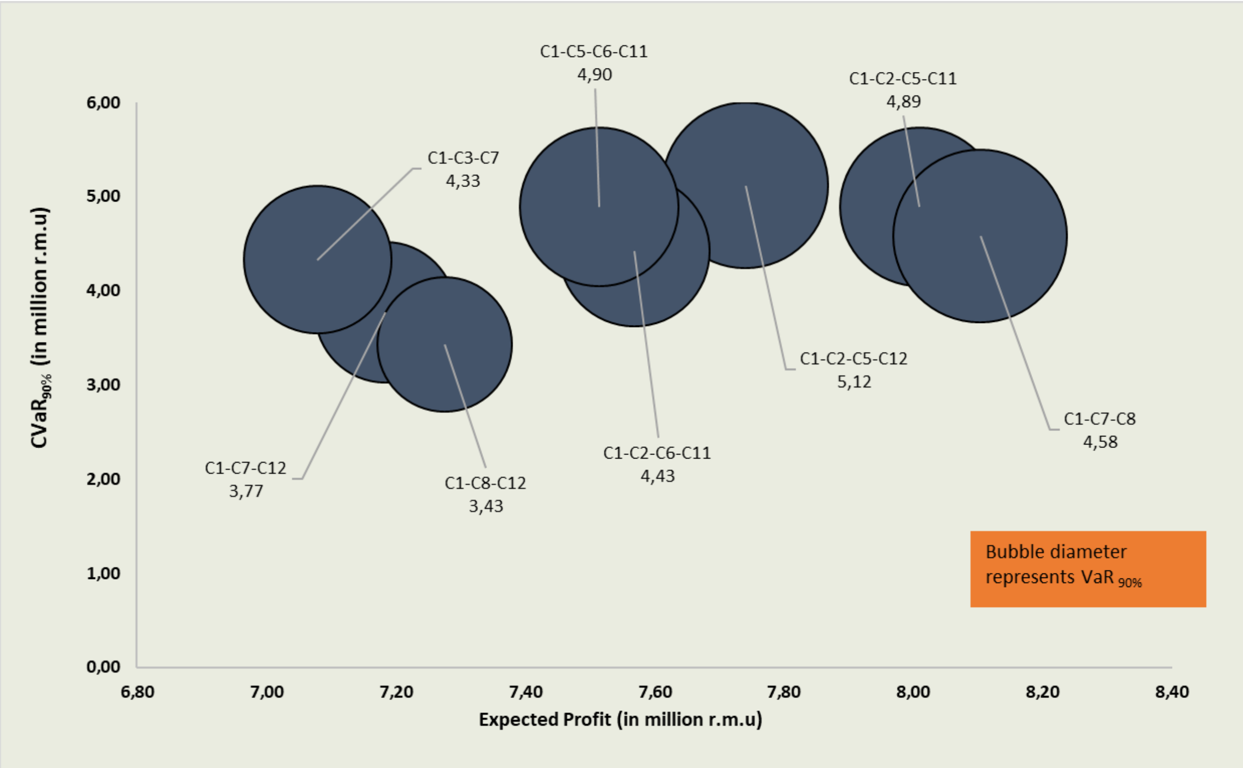

Figure 4.6 Expected profit, $CVaR_{90\%}$ and $VaR_{90\%}$ of the eight most promising contract combinations based on the expected profit

Table 4.4 Contract data

contracts	Contract availability / Product type	Products	Demand multiplier for each scenario and probability of realization			
			High	Target	Low	Fail
C1	Agreed/developed	1,2	1.2 (10%)	1 (80%)	0.8 (10%)	0 (0%)
C2	non agreed/developed	3,4	1.2 (10%)	1 (80%)	0.8 (10%)	0 (0%)
C3	non agreed/developed	5,6,7	1.2 (10%)	1 (80%)	0.8 (10%)	0 (0%)
C4	non agreed/developed	8,9,10	1.2 (10%)	1 (80%)	0.8 (10%)	0 (0%)
C5	non agreed/developed	11,12	1.2 (10%)	1 (80%)	0.8 (10%)	0 (0%)
C6	non agreed/developed	13,14	1.2 (10%)	1 (80%)	0.8 (10%)	0 (0%)
C7	non agreed/new	15,16,17	1.2 (15%)	1 (60%)	0.5 (20%)	0 (5%)
C8	non agreed/new	18,19,20	1.4 (20%)	1 (50%)	0.4 (20%)	0 (10%)
C9	non agreed/new	21,22,23	1.7 (25%)	1 (40%)	0.2 (15%)	0 (20%)
C10	non agreed/new	24,25,26	1.8 (15%)	1 (40%)	0.3 (15%)	0 (30%)
C11	non agreed/new	27,28	1.7 (20%)	1 (40%)	0.4 (0%)	0 (40%)
C12	non agreed/new	29,30	1.7 (5%)	1 (35%)	0.6 (15%)	0 (45%)

Table 4.5 Statistical measures of the initial and the reduced profit distribution of contract combination C1-C7-C8

	skewness	kurtosis	Stdev (10^5)	Mean (10^5)
Initial Distribution (64 scenarios)	0.2416	2.4924	2.3821	8.1300
Reduced Distribution (12 scenarios)	0.2341	2.3348	2.3809	8.0012

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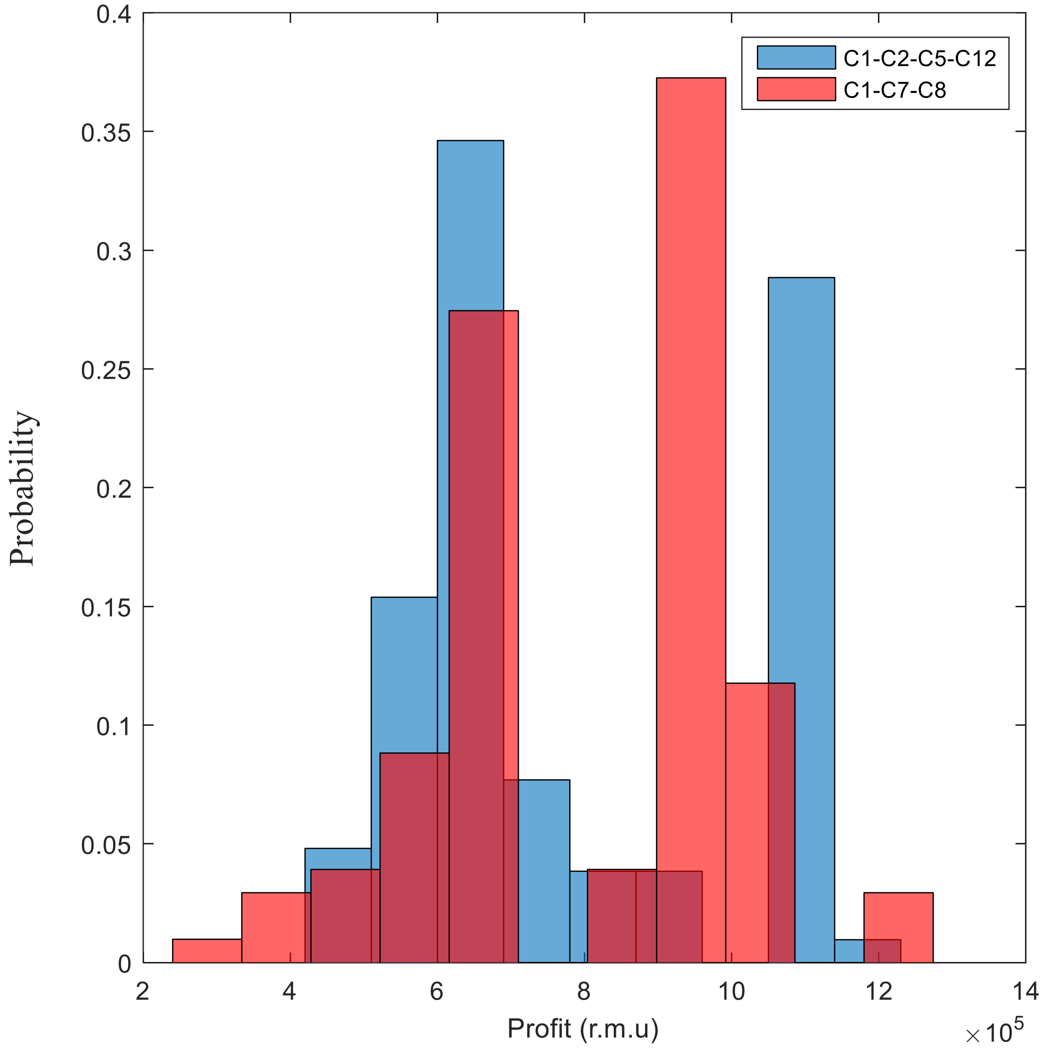

Figure 4.7 Profit distributions of contract combinations C1-C7-C8 and C1-C2-C5-C12

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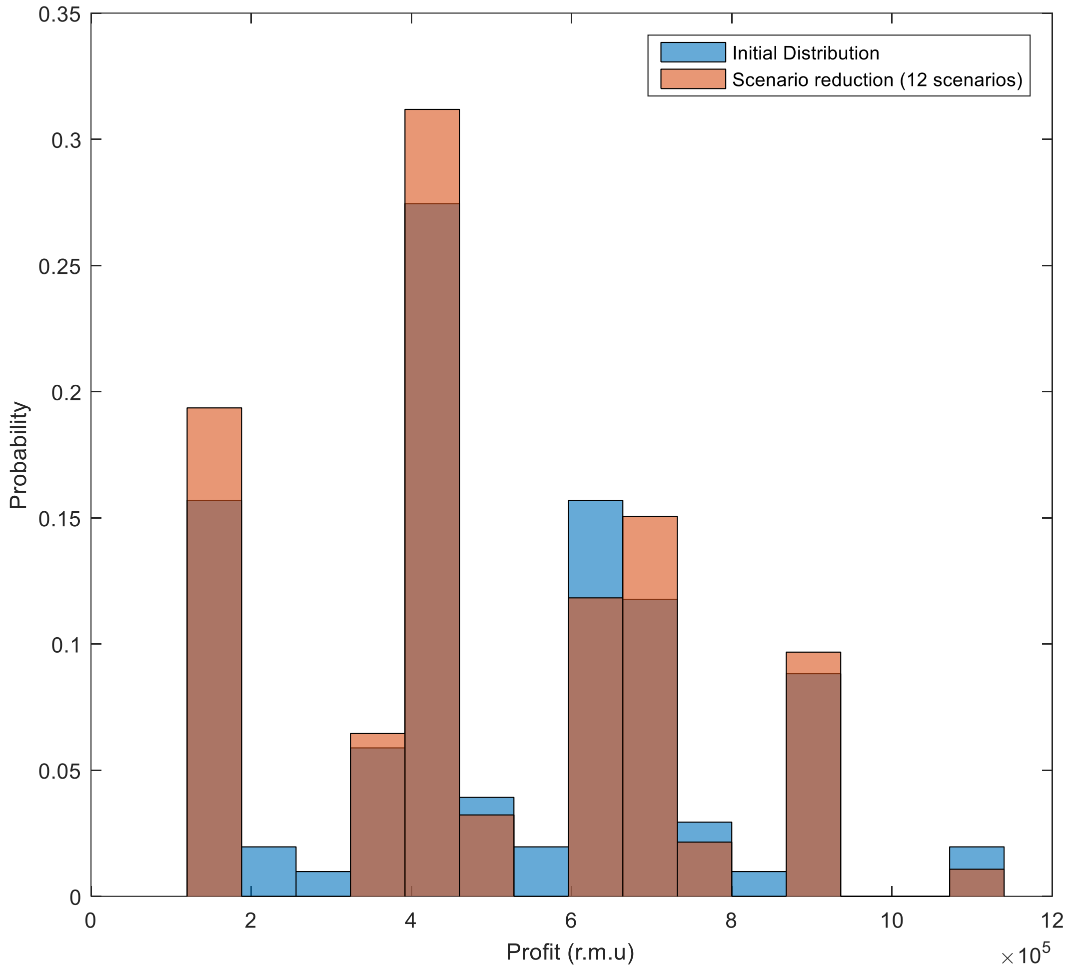

Figure 4.8 Initial and reduced profit distribution of contract combination C1-C7-C8

Finally, a detailed comparison between the initial and the reduced profit distribution of combination C1-C7-C8 is made, in order to assess the efficiency of the scenario reduction model. Both profit distributions are illustrated in Figure 4.8. Additional statistical measures such as kurtosis, skewness standard deviation and mean, are presented in Table 4.5 for both distributions. It is observed that the reduced profit distribution efficiently approximates the initial one as both upper and lower values of the tails are taken into account. Furthermore, the slight differences among the statistical measures also prove the effectiveness of the scenario reduction model.

Table 4.6 Summary of results for the ten most promising contract combinations based on the expected profit

Feasible Contract combination	Exp. Profit	$VaR_{90\%}$	$VaR_{95\%}$	$CVaR_{90\%}$	$CVaR_{95\%}$	Max. Profit
C1-C7-C8	8.10	6.03	4.34	4.58	3.98	12.64
C1-C2-C5-C11	8.01	5.08	5.08	4.89	4.70	11.73
C1-C2-C5-C12	7.74	5.50	5.50	5.12	4.74	11.75
C1-C2-C6-C11	7.57	4.55	4.55	4.43	4.31	11.11
C1-C5-C6-C11	7.51	5.05	5.05	4.90	4.74	10.55
C1-C8-C12	7.28	3.64	3.64	3.43	3.23	12.98
C1-C7-C12	7.18	3.96	3.96	3.77	3.59	12.96
C1-C3-C7	7.08	4.36	4.36	4.33	4.30	8.24
C1-C3-C12	7.04	4.40	4.40	4.11	3.82	10.77
C1-C5-C11	7.08	4.36	4.36	4.33	4.30	8.24

**The values represent millions of relative monetary units (r.m.u.)*

4.5.3 Large problem instance – Installation of an extra processing unit

Typically, process industries put huge efforts into improving their profit margins. Thus, production engineers often examine new alternative and more flexible plant layouts in order to increase productivity, and optimally allocate the available resources. In this subsection, a second plant layout is considered that includes an extra processing unit in the third processing stage. Detailed data for this problem are presented in Tables C16-C31 in the Appendix C.3. The problem is solved using the proposed solution algorithm.

Results illustrate that capacity expansions by installing an extra processing unit allows for signing more contracts. In particular, 9 additional contract combinations are defined as feasible after executing the first two steps of the solution algorithm. Results are summarized in Table C33 in the Appendix C.4., while the ten most profitable contract combinations are presented in Table 4.7. The installation of the new production line offers extra production capacity, and thus, more profitable combinations can be signed, such as C1-C6-C7-C11. However, the proposed capacity expansion does not allow for signing combinations with more than 4 contracts. The new plant layout also seems to be beneficial for both risk-neutral and risk-averse production policies. According to Table 4.7, the maximum expected profit is increased by 14.9% compared to the current plant layout. In particular, the combination C1-C6-C7-C11 leads to the maximum expected profit, which corresponds to 9.31 million r.m.u. Furthermore, the maximum $CVaR_{90\%}$ value is equal to 5.64 million r.m.u. This corresponds to an increase of 23% compared to the current layout.

Table 4.7 Summary of results for the ten most promising contract combinations based on the expected profit

Feasible Contract combination	Exp. Profit	$VaR_{90\%}$	$VaR_{95\%}$	$CVaR_{90\%}$	$CVaR_{95\%}$	Max. Profit
C1-C6-C7-C11	9.31	5.70	5.70	5.52	5.34	13.74
C1-C7-C8	8.12	6.03	4.34	5.64	4.09	12.64
C1-C2-C5-C11	8.01	5.08	5.08	4.89	4.70	11.73
C1-C7-C11	7.85	3.95	3.95	3.78	3.61	12.93
C1-C2-C5-C12	7.74	5.50	5.50	5.12	4.74	11.75
C1-C2-C6-C11	7.57	4.55	4.55	4.43	4.31	11.11
C1-C5-C6-C11	7.51	5.05	5.05	4.90	4.74	10.55
C1-C8-C12	7.39	3.64	3.64	3.43	3.23	14.34
C1-C8-C11	7.38	3.64	3.64	3.43	3.23	13.04
C1-C7-C12	7.20	3.96	3.96	3.77	3.59	13.27

**The values represent millions of relative monetary units (r.m.u.)*

Finally, noticeable improvements are also observed in several contract combinations. A representative comparison between the two layouts for contract combinations C1-C7-C8 and C1-C8-C12 is presented in Table 4.8. It is observed that the $CVaR_{90\%}$ is significantly increased by 23% in combination C1-C7-C8, while the maximum profit of combination C1-C8-C12 is also increased by 10.5%.

Table 4.8 Comparison between the expected profit $CVaR_{90\%}$ and the maximum profit of two representative contract combinations considering the two plant layouts

Feasible Contract combination	**Exp. Profit**	**$CVaR_{90\%}$**	**Max. Profit**	**Exp. Profit**	**$CVaR_{90\%}$**	**Max. Profit**
	Initial plant layout			New plant layout		
C1-C7-C8	8.10	4.58	12.64	8.12	5.64	12.64
C1-C8-C12	7.28	3.43	12.98	7.39	3.43	14.34

The values represent millions of relative monetary units (r.m.u.)

4.6 Conclusions

This work presents a systematic approach for the optimal contract selection problem of Contract Manufacturing Organizations (CMOs) under demand uncertainty. A rolling horizon framework is adapted for the integrated planning and scheduling of multi-stage batch facilities, typically met in the pharmaceutical industry. Multiple scenarios are considered to model uncertainty, while a three-stage solution algorithm is proposed to cope with large-scale problem instances. The first two steps evaluate the feasibility of each contract combination. . Both systematic and unsystematic risks are considered, depending on the product types of each contract. In the last stage of the algorithm, the integrated planning and scheduling problem is solved for all feasible combinations and all individual scenarios. A scenario reduction approach is utilized to decrease the total computational time. To assess the applicability of the proposed modelling framework, two different problem instances have been solved. The consideration of scheduling decisions can significantly enhance the accuracy of the modelling framework, and results illustrate that the proposed solution strategy can efficiently maximize the expected profit depending on the underlying risk tolerance. Furthermore, a capacity

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expansion of the plant leads to notable benefits for both risk-neutral and risk-averse production policies.

Nomenclature

Planning MILP model

Indices/Sets

$c \in C$	Contracts
$j \in J$	Production units
$p, p' \in P$	Products
$s \in S$	Processing stages
$w \in W$	Weeks

Subsets

$j \in JS_s$	Production units that are suitable for performing tasks of processing stage *s*, ($JS_s \subseteq J$)
$j \in PJ_p$	Production units that are suitable for processing product $p \in P$, ($PJ_p \subseteq J$)

Parameters

avl_s	Total available production time of stage *s*
bc_p	Backlog cost of product *p*
$cap_{p,s}$	Inventory capacity of product *p*, in stage *s*
$cl_{p,j}$	Average cleaning time for product *p,* in unit *j*
$d_{p,s,w}$	Demand of product *p*, at stage *s*, at the end of week *w*
fr_p	Fixed raw material cost of product *p*

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$fx_{p,j}$	Fixed processing time of product *p*, in unit *j*
h	Time horizon of each week *w*
ic_p	Inventory cost of product *p*
in_c	Initial payment of contract *c*
pr_p	Selling price of product *p*
q_j^{max}	Maximum capacity of unit *j*
q_j^{min}	Minimum capacity of unit *j*
qc_p	Operational cost of product *p*
qw_j^{min}	Minimum weekly production of unit *j*
qw_j^{max}	Maximum weekly production of unit *j*
rc_p	Variable raw material cost of product *p*
$vt_{p,j}$	Variable processing time of product *p*, in unit *j*
wc	Maximum storage capacity of the warehouse
μ_s	Sequencing factor for stage *s*

Variables

$B_{p,s,w}$	Backlog of product *p*, at stage *s*, in week *w*
$I_{p,s,w}$	Inventory of product *p*, at stage *s*, at the end of week *w*
$N_{p,j,w}$	Integer variable denoting the minimum number of batches of product *p*, that must be processed in unit *j*, in week *w*
$T_{p,j,w}$	Processing time of product *p*, in unit *j*, in week *w*

$Q_{p,j,w}$ production amount of product p, in unit j, in week w

$WV_{p,j,w}$ Binary variable that takes the value 1 only if a product p, is allocated to unit j, in week w

Scheduling MILP model

Indices/Sets

$b, b' \in B$ Product batches

$j \in J$ Production units

$p, p' \in P$ Products

$s \in S$ Processing stages

Subsets

$j \in JS_s$ Production units that are suitable for performing tasks of processing stage s, ($JS_s \subseteq J$)

$j \in PJ_p$ Production units that are suitable for processing product $p \in P$, ($PJ_p \subseteq J$)

Parameters

bc_p Backlog cost of product p

$cap_{p,s}$ Inventory capacity of product p, in stage s

$ch_{p,p'}$ Changeover time between product p and p'

$dm_{p,s}$ Demand of product p, at stage s

fr_p Fixed raw material cost of product p

$fx_{p,j}$ Fixed processing time of product p, in unit j

h The time horizon of each week w

ic_p	Inventory cost of product *p*
$ininv_{p,s}$	Initial inventory of product *p,* at stage *s*
iuc	Inventory underproduction cost
pr_p	Selling price of product *p*
puc	Underproduction cost
q_j^{max}	Maximum capacity of unit *j*
q_j^{min}	Minimum capacity of unit *j*
qc_p	Operational cost of product *p*
$tinv_{p,s}$	Total inventory target of product *p*, at stage *s*
$tprod_{p,s}$	Total production target of product *p*, at stage *s*
trs_p	Unit transfer rate of a product *p,* between consecutive stages
$vt_{p,j}$	Variable processing time of product *p,* in unit *j*
wc	Maximum storage capacity of the warehouse

Continuous Variables

$BA_{p,s}$	Backlog of product *p,* at stage *s*
$CT_{b,s}$	Completion time of batch *b*, at stage *s*
$INV_{p,s}$	Inventory of product *p,* in stage *s,* at the end of time horizon
$IU_{p,s}$	Inventory underproduction of product *p,* at stage *s*
$PU_{p,s}$	Total underproduction of product *p,* at stage *s*
$QB_{b,p,s}$	Batch size of batch *b*, of product *p*, at stage *s*
$QBV_{b,p,j}$	Variable batch size of batch *b*, of product *p*, in unit *j*

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$ST_{b,s}$	Starting time of batch *b*, at stage *s*
$TP_{b,s}$	Processing time of batch *b,* at stage *s*
$UINV_{b,p,s}$	Inventory used for batch *b,* of product *p,* at stage *s*
$WT_{b,s}$	Waiting time of product *p,* at stage *s*

Binary Variables

$XB_{b,b',j}$	Takes the value 1 only if batch *b′* is operated after batch *b* in unit *j*
$YII_{b,p,s}$	Takes the value 1 only if batch *b* of product *p* is fulfilled by stored amount
$YP_{b,p}$	Takes the value 1 only if batch *b* is allocated to product *p*
$YU_{b,p,j}$	Takes the value 1 only if batch *b,* of product *p,* is allocated to the processing unit *j*

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5

Conclusions and future research

5.1 Conclusions

The objective of this thesis has been to develop optimization-based frameworks for the short-term scheduling of complex industrial processes and the integrated planning and scheduling problem under uncertainty. Hence, several MILP models have been developed for the short-term scheduling of continuous make-and-pack process, typically met in food and consumer goods industries. Moreover, novel MILP-based decomposition algorithms have been investigated to handle complex real-life industrial problems in an efficient manner. Results illustrate that the application of the proposed computer aided frameworks of this thesis to industrial scheduling problems, can lead to noticeable economic, operational and environmental benefits.

In chapter 2, the scheduling of single-stage continuous industrial facilities is studied. The problem mainly focuses on the packing stage, which typically constitutes the production bottleneck in most industries. Two MILP models have been proposed for the scheduling of packing stage, while constraints related to the previous stages are taken into account to ensure the feasibility of solutions. Although various research contributions have been proposed for this problem, the majority of them has not been applied in complex, large scale problems. To face this challenge, two decomposition algorithms have been developed. Both approaches consist of two individual steps and rely on the iterative solution of the MILP models. The first step, aims to generate an initial feasible solution which can be further improved via the second step. Therefore, the initial complex problems become tractable, and good quality solutions can be obtained within acceptable CPU time. The proposed optimization strategies aim to minimize the total changeover time, while different objectives (such as makespan minimization) can also be considered, depending on the current need of decision-makers. In order to assess the applicability and the efficiency of the proposed models and solution strategies, several indicative case studies of a multinational consumer goods industry have been considered. An efficient tool has also been developed in collaboration with the plant engineers to facilitate data exchange through direct communication of MILP models and the ERP systems of the plant. Results have been fully validated by the plant operators, and detailed comparisons with manually generated schedules or simulation tools have been made. Significant benefits have been achieved. In particular, the obtained solutions can dramatically decrease the total changeover time by even 25% on a weekly basis, and therefore, productivity can be increased by 1.5-2%, depending on the problem case. The proposed solution approaches can be utilized as the main core of an automated optimization tool that assists decision-makers in obtaining good quality solutions under the current dynamic industrial environment. Furthermore, this work provides indisputable evidence for the benefits of using optimization-based frameworks for challenging industrial problems.

Chapter 3 forms a direct continuation of the previous chapter, as it examines the production scheduling of multistage continuous, make-and-pack processes with flexible storage equipment and recycle option. The synchronization of production stages in continuous processes is usually a challenging problem. Hence, the utilization of intermediate buffers allows for extra flexibility and aims to increase the total throughput. Since the continuous make-and-pack layout is common in several industrial sectors, multiple research contributions have already proposed solution methods to address this problem. However, most of them rely on discrete-time representations, and as a result, the corresponding MILP models become intractable when considering large-scale problems. Also, recent optimization approaches rely on weak assumptions often leading to suboptimal or even infeasible solutions. A novel continuous time MILP model is proposed for the problem at hand to fill this gap. A new set of binary variables is introduced to satisfy mass balance constraints efficiently. Extending previously proposed mathematical frameworks, multiple lots of the same recipe can be stored simultaneously in a buffer tank.

Moreover, a key component of the modelling framework is the consideration of byproduct recycling streams in order to enhance the use of raw materials and resources. A two-stage decomposition algorithm is proposed for the solution of larger problems. Several case studies, inspired by consumer goods industries, were solved to illustrate the application of the proposed modelling frameworks. Multiple plant layouts and different storage policies have been examined. Results show that the plant's economic operation is significantly improved due to the flexible storage policy.

Chapter 4 addresses the optimal contract selection problem of Contract Manufacturing Organizations (CMOs), under uncertainty in the pharmaceutical industry. Under the current climate of business globalization, large multinational pharmaceutical companies often decide to outsource part of the manufacturing process to other industrial facilities under contract agreements. These companies are known as Contract Manufacturing Organizations. Since pharmaceutical products are described by highly volatile demand, CMOs must carefully choose the optimal contract mixture to sign, in order to maximize their profit margin while mitigating their exposure to risk. To face this challenging problem, a rolling horizon framework is adapted for the integrated planning and scheduling of multi-stage batch facilities, typically met in the pharmaceutical industry. Several discrete scenarios are examined to model demand uncertainty. Both systematic and unsystematic risks are considered, depending on the product types of each contract. A solution algorithm that consists of three individual steps is proposed to tackle realistic problems with multiple contracts, while a scenario reduction MILP model is utilized to decrease the total computational time. The feasibility of each contract combination is assessed via the first two steps of the solution algorithm. In the last stage, the rolling horizon framework is applied to solve the integrated planning and scheduling problem for all feasible contract combinations and all individual scenarios. To assess the applicability and efficency of the proposed modelling framework, different case studies have been examined. Results illustrate that the proposed solution strategy leads to notable benefits for both risk-neutral and risk-averse policies. Considering a given risk tolerance, the proposed modelling framework can efficiently maximize the expected profit of Contract Manufacturing Organizations.

5.2 Main contributions

In summary, the main contributions of this thesis are presented below:

- Two MILP-based mathematical frameworks have been developed for the optimal short-term production scheduling of continuous processes.

- Efficient solution strategies are presented for the scheduling of continuous processes based on the proposed MILP models and decomposition algorithms to address large-scale case studies. The proposed approaches can assist production engineers and decision-makers towards fast generation of improved schedules.

- The proposed modelling frameworks have been applied to the scheduling problem of a real-life consumer goods industry. An efficient tool has been developed by plant engineers based on the proposed MILP-based frameworks, and comparisons with manually generated schedules have been realized. Solutions have been fully validated by the industry, and significant gains have been realized in terms of changeover minimization and productivity improvement.

- Chapter 2 also highlights the potential benefits of using optimization-based techniques and the impact of scheduling optimization on the overall performance of industrial facilities. The introduction of efficient solution strategies and their implementation in real and complex scheduling problems is an essential step toward closing the existing gap between scientific knowledge and industrial reality.

- A novel MILP model has been developed for the optimal scheduling of multistage continuous make-and-pack industries with flexible storage tanks. Furthermore, a two-stage decomposition algorithm has been proposed to face large-scale problems. Compared with alternative modelling approaches that rely on weak assumptions, the proposed framework can efficiently generate feasible and nearly optimal solutions for real-life scheduling problems.

- Considering byproduct recycling streams in consumer goods industries constitutes an open challenging problem. Hence, this thesis contributes to the decrease of the current gap. Furthermore, results prove that byproduct recycling constraints allow for waste reduction and better utilization of resources.

- The contract selection problem of Contract Manufacturing Organizations in the secondary pharmaceutical industry under demand uncertainty has been introduced in

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the open literature. An integrated planning and scheduling approach has been developed for multistage batch facilities, based on the rolling horizon framework. A scenario-based approach has been utilized to model demand uncertainty, while both systematic and unsystematic risks have been considered. The development of a solution strategy allows for considering real-life problem instances with multiple scenarios.

- In comparison with aggregated planning frameworks existing in the open literature, the consideration of scheduling decisions can improve the accuracy and ensure the feasibility of obtained solutions. The developed mathematical framework can facilitate Contract Manufacturing Organizations to maximize their profits while mitigating the underlying risk exposure.

5.3 Recommendations for future directions

A range of issues requiring further investigation have been revealed in the course of this thesis. In particular:

- The models proposed in Chapter 2 are mainly focused on short-term scheduling. Lot-sizing decisions are pre-defined, and decisions include only unit to task assignment, sequencing and timing of tasks. A promising direction for future extension would be the development of an integrated planning and scheduling optimisation framework, by including lot-sizing decisions and inventory constraints.
- This thesis aims to the development of offline scheduling models. However, production scheduling is highly dynamic. Frequent late-order arrivals, or sudden order cancelations, impose the need of several modifications in the initial production schedule on a daily basis. Hence, the consideration of real-time uncertainties in the developed models is critical for their application in practice. A computationally efficient method is the introduction of a reactive scheduling approach that employs the rolling-horizon framework.
- Further extension regarding the optimisation-based approach presented in chapter 3 seems a promising research task. The proposed MILP model is focused on industrial layouts that consists of two production stages. Future

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works are envisaged to focus on extending the proposed approach, by considering multiple production stages with flexible storage tanks.

- Room for improvement exists regarding the solution strategy developed for the for the optimal contract selection problem of Contract Manufacturing Organizations (CMOs). The proposed modelling framework considers the planning and scheduling problem of multistage batch facilities. However, recent advances in manufacturing technology have prompted several pharmaceutical industries, to adopt continuous manufacturing. According to regulatory agencies, such as FDA, continuous manufacturing could address drug shortages and recalls. Hence, future works could focus on modelling both batch and continuous processes.
- Another direction for future work is the consideration of multiple types of uncertainty, associated with the availability and prices of raw materials. Under the current global supply chain crisis and the shortage of raw materials, the consideration of the integrated contract and supplier selection problem constitutes a high priority for decision-makers.

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Research Outputs

Herein, an overview of the research outputs of this dissertation is provided.

Peer-reviewed journal publications

1. Georgiadis, G.P., Elekidis, A.P., Georgiadis, M.C., 2019. Optimization-Based Scheduling for the Process Industries: From Theory to Real-Life Industrial Applications. *Processes* 7, 438. https://doi.org/10.3390/pr7070438

2. Elekidis, A.P., Corominas, F., Georgiadis, M.C., 2019. Production Scheduling of Consumer Goods Industries. *Industrial and Engineering Chemistry Research* 58, 23261–23275. https://doi.org/10.1021/acs.iecr.9b04907

3. Elekidis, A.P., Georgiadis, M.C., 2021. Production scheduling of flexible continuous make-and-pack processes with byproducts recycling. *International Journal of Production Research* 1–23. https://doi.org/10.1080/00207543.2021.1920058

4. Elekidis, A.P., Georgiadis, M.C., 2021. Optimal Contract Selection for Contract Manufacturing Organizations in the Secondary Pharmaceutical Industry. *Computers and Chemical Engineering (*Under review)

International conference proceedings

1. Apostolos P. Elekidis, Vasilios Yfantis, Francesc Corominas, Michael C. Georgiadis and Sebastian Engell (2019). Optimal Production Scheduling of Packaged Goods Industries. 12th European Congress of Chemical Engineering, ECCE12; September 15-19, Florence, Italy

2. Apostolos P. Elekidis, Francesc Corominas, Michael C. Georgiadis (2019). Optimal short-term Scheduling of Industrial Packing Facilities. Computer-Aided Chemical Engineering, 46, 1183-1188

3. Apostolos P. Elekidis, Georgios P. Georgiadis, Michael C. Georgiadis (2021). Production scheduling of continuous make-and-pack processes with byproducts recycling. Computer-Aided Chemical Engineering, 50, 1727-1732

4. Apostolos P. Elekidis and Michael C. Georgiadis (2022) Optimal Contract Selection for Contract Manufacturing Organisations in the Pharmaceutical Industry Under Uncertainty. In 32nd European Symposium on Computer-Aided

Process Engineering (ESCAPE 32), June 12-15, 2022, Toulouse, France (Accepted).

National conference

- Apostolos P. Elekidis, Michael C. Georgiadis (2019). Optimal Production Scheduling of Continuous process in packaged goods industries. PSCCE 12, *12th* Panhellenic Scientific Conference of Chemical Engineering, Athens, Greece, May 29-31

- Apostolos P. Elekidis, Michael C. Georgiadis (2022). Optimal Contract Appraisal for Contract Manufacturing Organisations in the Pharmaceutical Industry. PSCCE 13, 13rd Panhellenic Scientific Conference of Chemical Engineering, Patras, Greece, June 2-4

Appendix A

Pseudocodes for the individual steps of the solution algorithm

Algorithm 1. Pseudo-code for iterative procedure in constructive step
Set step = 5, initial = 5, pos(i) parameter, $i \in I^{IN}=\emptyset$;
FOR k= initial to $\lvert I \rvert$ by step
LOOP $i \in I$
IF pos(i) $\leq$ k
$I^{IN} = I^{IN}$ U $\{i\}$
END IF
END LOOP
SOLVE MILP model
Fix $Y_{i,j}$ & $X_{i',i,j}$ binary variables
END FOR
SAVE initial solution SC
SAVE total CPU time

Algorithm 2. Pseudo-code for iterative procedure in improvement step 1
Set $i \in I^{IDN}=\emptyset;$
LOOP s $\in S$
LOOP $i \in I$
LOOP $i' \in I : i' \neq i$
IF $ID_{i,i',s} > 0$
$I^{IDN} = I^{IDN}$ U $\{i\}$
END IF
END LOOP
END LOOP
END LOOP
CLEAR all variables related to $i \in I^{IDN}$ (e.g., $Y_{i,j}$, $X_{i',i,j}$, etc.)
SOLVE MILP model and obtain solution *SD*
SAVE total CPU time
IF *SD* <*SC*
SC=SD
Save Solution (e.g. save *SC*, $Y_{i,j}$, $X_{i',i,j}$, etc.)
END IF

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Algorithm 3. Pseudo-code for iterative procedure in improvement step 2

Set step = 5, initial = 5, iter=1, pos (i) parameter, $i \in I^{REIN}$=$\emptyset$;
FOR k= initial to $\|I\|$ by step
LOOP s $\in S$
LOOP $i \in I$
LOOP $i' \in I : i' \neq i$
IF $L_{i,i',s} > 0$
I^{REIN}=I^{REIN} U $\{i\}$
END IF
END LOOP
END LOOP
END LOOP
 	
LOOP $i \in I$
IF (pos(i) < k) AND (pos(i) >k-step)
I^{REIN}=I^{REIN} U $\{i\}$
END IF
END LOOP
CLEAR all variables related to I^{REIN} (e.g., $Y_{i,j}$, $X_{i',i,j}$, etc.)
SOLVE MILP model and obtain solution SR(iter)
SAVE total CPU
IF SR(iter) <SC
SC= SR(iter)
SAVE Solution (e.g. save SC , $Y_{i,j}$, $X_{i',i,j}$, etc.)
END IF
iter=iter +1
IF total CPU> lt
k= $\|I\|$+1
The algorithm is terminated
END IF
END FOR

`

Appendix B

Appendix B presents the data for Chapter 3. The data for the case 1 are summarized in Tables B1 – B6.

Table B1. Products demand (parameter $QALL_i$)

Product	$QALL_i$ (kg)	Product	$QALL_i$ (kg)	Product	$QALL_i$ (kg)	Product	$QALL_i$ (kg)
1	1620	**26**	1254	**51**	1620	**76**	1254
2	1200	**27**	984	**52**	1200	**77**	984
3	1620	**28**	1353	**53**	1620	**78**	1353
4	1680	**29**	864	**54**	1680	**79**	864
5	936	**30**	2052	**55**	936	**80**	2052
6	540	**31**	1140	**56**	540	**81**	1140
7	1050	**32**	780	**57**	1050	**82**	780
8	420	**33**	294	**58**	420	**83**	294
9	1050	**34**	688,5	**59**	1050	**84**	688,5
10	1254	**35**	496	**60**	1254	**85**	496
11	1080	**36**	450,25	**61**	1080	**86**	450,25
12	1080	**37**	404,5	**62**	1080	**87**	404,5
13	717,6	**38**	358,75	**63**	717,6	**88**	358,75
14	945	**39**	313	**64**	945	**89**	313
15	178,2	**40**	267,25	**65**	178,2	**90**	267,25
16	780	**41**	221,5	**66**	780	**91**	221,5
17	294	**42**	780	**67**	294	**92**	780
18	688,5	**43**	294	**68**	688,5	**93**	294
19	1827	**44**	688,5	**69**	1827	**94**	688,5
20	1170	**45**	496	**70**	1170	**95**	496
21	1566	**46**	450,25	**71**	1566	**96**	450,25
22	443,7	**47**	780	**72**	443,7	**97**	780
23	1218	**48**	294	**73**	1218	**98**	294
24	2520	**49**	688,5	**74**	2520	**99**	688,5
25	1140	**50**	496	**75**	1140	**100**	496

Table B2. Products due dates (parameter DD_i)

Product	DD_i (hours)	Product	DD_i (hours)	Product	DD_i (hours)	Product	DD_i (hours)
1	24	**26**	80	**51**	100	**76**	144
2	24	**27**	80	**52**	100	**77**	144
3	24	**28**	80	**53**	100	**78**	144
4	24	**29**	80	**54**	100	**79**	144
5	24	**30**	80	**55**	100	**80**	144
6	24	**31**	80	**56**	100	**81**	144
7	24	**32**	80	**57**	100	**82**	144
8	24	**33**	80	**58**	100	**83**	144
9	24	**34**	80	**59**	100	**84**	168
10	24	**35**	80	**60**	120	**85**	168
11	48	**36**	80	**61**	120	**86**	168
12	48	**37**	80	**62**	120	**87**	168
13	48	**38**	80	**63**	120	**88**	168
14	48	**39**	80	**64**	120	**89**	168
15	48	**40**	80	**65**	120	**90**	168
16	48	**41**	80	**66**	120	**91**	168
17	48	**42**	80	**67**	120	**92**	168
18	48	**43**	80	**68**	120	**93**	168
19	48	**44**	80	**69**	120	**94**	168
20	48	**45**	80	**70**	120	**95**	168
21	48	**46**	80	**71**	120	**96**	168
22	48	**47**	80	**72**	120	**97**	168
23	48	**48**	80	**73**	120	**98**	168
24	48	**49**	80	**74**	144	**99**	168
25	48	**50**	80	**75**	144	**100**	168

`

Table B3. Products recipe type (parameter F_i)

Product	F_i	Product	F_i	Product	F_i	Product	F_i
1	1	**26**	5	**51**	1	**76**	5
2	1	**27**	5	**52**	1	**77**	5
3	1	**28**	6	**53**	1	**78**	6
4	1	**29**	6	**54**	1	**79**	6
5	1	**30**	6	**55**	1	**80**	6
6	2	**31**	6	**56**	2	**81**	6
7	2	**32**	7	**57**	2	**82**	7
8	2	**33**	7	**58**	2	**83**	7
9	2	**34**	7	**59**	2	**84**	7
10	2	**35**	7	**60**	2	**85**	7
11	3	**36**	7	**61**	3	**86**	7
12	3	**37**	7	**62**	3	**87**	7
13	3	**38**	7	**63**	3	**88**	7
14	3	**39**	7	**64**	3	**89**	7
15	3	**40**	7	**65**	3	**90**	7
16	4	**41**	8	**66**	4	**91**	8
17	4	**42**	8	**67**	4	**92**	8
18	4	**43**	8	**68**	4	**93**	8
19	4	**44**	8	**69**	4	**94**	8
20	4	**45**	8	**70**	4	**95**	8
21	4	**46**	8	**71**	4	**96**	8
22	5	**47**	9	**72**	5	**97**	9
23	5	**48**	9	**73**	5	**98**	9
24	5	**49**	9	**74**	5	**99**	9
25	5	**50**	9	**75**	5	**100**	9

`

Table B4. Products maximum throughput at stage s=1 ($R_{i,1}$)

Product	$R_{i,1}$ (kg/hr)	Product	$R_{i,1_i}$ (kg/hr)	Product	$R_{i,1}$ (kg/hr)	Product	$R_{i,1}$ (kg/hr)
1	201	**26**	201	**51**	201	**76**	201
2	201	**27**	201	**52**	201	**77**	201
3	201	**28**	201	**53**	201	**78**	201
4	201	**29**	201	**54**	201	**79**	201
5	350	**30**	201	**55**	292	**80**	201
6	369	**31**	201	**56**	308	**81**	201
7	379	**32**	201	**57**	316	**82**	201
8	340	**33**	201	**58**	284	**83**	201
9	369	**34**	201	**59**	308	**84**	201
10	408	**35**	201	**60**	340	**85**	201
11	369	**36**	292	**61**	308	**86**	292
12	369	**37**	308	**62**	308	**87**	308
13	201	**38**	316	**63**	201	**88**	316
14	201	**39**	284	**64**	201	**89**	284
15	201	**40**	201	**65**	201	**90**	201
16	201	**41**	201	**66**	201	**91**	201
17	201	**42**	201	**67**	201	**92**	201
18	201	**43**	201	**68**	201	**93**	201
19	369	**44**	292	**69**	308	**94**	292
20	408	**45**	308	**70**	340	**95**	308
21	369	**46**	316	**71**	308	**96**	316
22	369	**47**	284	**72**	308	**97**	284
23	201	**48**	201	**73**	201	**98**	201
24	201	**49**	201	**74**	201	**99**	201
25	201	**50**	201	**75**	201	**100**	201

`

Table B5. Products maximum throughput at stage s=2 ($\boldsymbol{R}_{i,2}$)

Product	$R_{i,2}$ (kg/hr)	Product	$R_{i,2}$ (kg/hr)	Product	$R_{i,2}$ (kg/hr)	Product	$R_{i,2}$ (kg/hr)
1	369	**26**	308	**51**	308	**76**	308
2	408	**27**	261	**52**	340	**77**	261
3	369	**28**	261	**53**	308	**78**	261
4	369	**29**	235	**54**	308	**79**	235
5	201	**30**	248	**55**	201	**80**	248
6	201	**31**	248	**56**	201	**81**	248
7	201	**32**	308	**57**	201	**82**	308
8	201	**33**	340	**58**	201	**83**	340
9	284	**34**	308	**59**	284	**84**	308
10	292	**35**	308	**60**	292	**85**	308
11	211	**36**	201	**61**	211	**86**	201
12	227	**37**	201	**62**	227	**87**	201
13	369	**38**	201	**63**	308	**88**	201
14	408	**39**	201	**64**	340	**89**	201
15	369	**40**	308	**65**	308	**90**	308
16	369	**41**	340	**66**	308	**91**	340
17	253	**42**	308	**67**	211	**92**	308
18	282	**43**	308	**68**	235	**93**	308
19	235	**44**	201	**69**	235	**94**	201
20	235	**45**	201	**70**	235	**95**	201
21	243	**46**	201	**71**	243	**96**	201
22	211	**47**	201	**72**	211	**97**	201
23	219	**48**	308	**73**	219	**98**	308
24	211	**49**	340	**74**	211	**99**	340
25	219	**50**	308	**75**	219	**100**	308

`

Table B6. Products allocation flexibility

Products	Units						Products	Units					
	Formulation stage			Packing stage				Formulation stage			Packing stage		
	1	2	3	4	5	6		1	2	3	4	5	6
1	1	1	1	1	0	1	**51**	1	1	1	1	0	1
2	1	1	1	1	1	1	**52**	1	1	1	1	1	1
3	1	1	1	1	1	1	**53**	1	1	1	1	1	1
4	1	1	1	1	1	1	**54**	1	1	1	1	1	1
5	1	1	1	1	1	1	**55**	1	1	1	1	1	1
6	1	1	1	1	1	1	**56**	1	1	1	1	1	1
7	1	1	1	1	1	0	**57**	1	1	1	1	1	0
8	1	1	1	0	1	0	**58**	1	1	1	0	1	0
9	1	1	1	0	1	1	**59**	1	1	1	0	1	1
10	1	1	1	0	1	1	**60**	1	1	1	0	1	1
11	1	1	1	1	0	1	**61**	1	1	1	1	0	1
12	1	1	1	1	0	1	**62**	1	1	1	1	0	1
13	1	1	1	1	1	1	**63**	1	1	1	1	1	1
14	1	1	1	1	1	1	**64**	1	1	1	1	1	1
15	1	1	1	1	1	1	**65**	1	1	1	0	1	1
16	1	1	1	1	1	1	**66**	1	1	1	0	1	1
17	1	1	1	1	1	1	**67**	1	1	1	0	1	1
18	1	1	1	1	1	1	**68**	1	1	1	1	1	1
19	1	1	1	1	1	1	**69**	1	1	1	1	1	1
20	1	1	1	1	1	1	**70**	1	1	1	1	1	1
21	1	1	1	1	1	1	**71**	1	1	1	1	1	1
22	1	1	1	1	1	1	**72**	1	1	1	1	1	1
23	1	1	1	1	1	1	**73**	1	1	1	1	1	1
24	1	1	1	1	0	1	**74**	1	1	1	1	0	1
25	1	1	1	1	0	1	**75**	1	1	1	1	0	1
26	1	1	1	1	0	1	**76**	1	1	1	1	0	1
27	1	1	1	1	0	1	**77**	1	1	1	1	0	1

`

28	1	1	1	1	0	1	**78**	1	1	1	1	0	1
29	1	1	1	1	0	1	**79**	1	1	1	1	0	1
30	1	1	1	1	0	1	**80**	1	1	1	1	0	1
31	1	1	1	1	0	1	**81**	1	1	1	1	0	1
32	0	1	1	1	1	1	**82**	0	1	1	1	1	1
33	0	1	1	1	1	1	**83**	0	1	1	1	1	1
34	0	1	1	1	1	1	**84**	0	1	1	1	1	1
35	0	1	1	1	1	1	**85**	0	1	1	1	1	1
36	0	1	1	1	1	1	**86**	0	1	1	1	1	1
37	0	1	1	1	1	1	**87**	0	1	1	1	1	1
38	0	1	1	1	1	1	**88**	0	1	1	1	1	1
39	0	1	1	1	1	1	**89**	0	1	1	1	1	1
40	0	1	1	1	1	1	**90**	0	1	1	1	1	1
41	1	1	1	1	1	1	**91**	1	1	1	1	1	1
42	1	1	1	0	1	1	**92**	1	1	1	0	1	1
43	1	1	1	0	1	1	**93**	1	1	1	0	1	1
44	1	1	1	0	1	1	**94**	1	1	1	0	1	1
45	1	1	1	1	1	1	**95**	1	1	1	1	1	1
46	1	1	1	1	1	1	**96**	1	1	1	1	1	1
47	1	1	1	1	1	1	**97**	1	1	1	1	1	1
48	1	1	1	1	1	1	**98**	1	1	1	1	1	1
49	1	1	0	1	1	1	**99**	1	1	1	1	1	1
50	1	1	0	1	1	1	**100**	1	1	1	1	1	1

`

Appendix C

C.1. Scenario reduction model

In this section, a scenario reduction MILP model, proposed by Li and Floudas, (2014), is presented. The model relies on the sets, parameters, and variables, listed in section C.1.1. The model objective function and the constraints are also presented in section C.1.2.

C.1.1. Nomenclature

Indices/Sets

$s, s' \in S$ Scenarios

Parameters

$c_{s,s'}$ Distance between scenario s and s'

p_s^{orig} Probability of scenario s in original discrete distribution

f^{max} Maximum objective value of all scenarios in original discrete distribution

f^{exp} Expected objective value of all scenarios in original discrete distribution

f^{min} Minimum objective value of all scenarios in original discrete distribution

f_s^* Optimal objective value under scenario s in original discrete distribution

N Number of scenarios to be removed

Continuous Variables

DIS_s	Minimum distance of all remaining scenarios to a removed scenario *s*
P_s^{orig}	Probability of scenario *s* in original discrete distribution
$V_{s,s'}$	Takes the value 1 only if scenario *s* is removed and assigned to scenario *s′*
FE^{max}	absolute error between the best objective value of original and reduced distribution
FE^{exp}	absolute error between the expected objective value of original and reduced distributions
FE^{min}	absolute error between the worst objective value of original and reduced distributions
FS^{max}	Maximum objective value of the reduced distribution of the remaining scenarios
FS^{exp}	Expected objective value of the reduced distribution of the remaining scenarios
FS^{min}	Minimum objective value of the reduced distribution of the remaining scenarios

Binary Variables

Y_s^{max}	Takes the value 1 only if scenario *s,* corresponds to the new maximum objective among the selected scenarios
Y_s^{min}	Takes the value 1 only if scenario *s,* corresponds to the new minimum objective among the selected scenarios
Y_s	Takes the value 1 only if scenario *s* is removed

`

C.1.2. MILP scenario reduction model

$$\sum_{s} Y_s = N \tag{C1}$$

$$\sum_{s'} V_{s,s'} \geq Y_s \quad \forall s \in S \tag{C2}$$

$$0 \leq V_{s,s'} \leq 1 - Y_{s'} \quad \forall s \in S, s' \in S \tag{C3}$$

$$DIS_s = \sum_{s'} V_{s,s'} c_{s,s'} \quad \forall s \in S \tag{C4}$$

$$DIS_s \leq Y_s f^{max} \quad \forall s \in S \tag{C5}$$

$$\sum_{s'} V_{s,s'} \leq 1 \quad \forall s \in S \tag{C6}$$

$$PN_{s'} = (1 - Y_{s'}) p_{s'}^{orig} + \sum_{s} V_{s,s'} p_s^{orig} \quad \forall s' \in S \tag{C7}$$

$$FS^{exp} = \sum_{s} PN_s f_s^* \tag{C8}$$

$$FS^{max} = \sum_{s} Y_s^{max} f_s^* \tag{C9}$$

$$FS^{max} \geq (1 - Y_s) f_s^* + Y_s f^{min} \quad \forall s \in S \tag{C10}$$

$$\sum_{s} Y_s^{max} = 1 \tag{C11}$$

$$Y_s^{max} \leq 1 - Y_s \tag{C12}$$

$$FS^{min} = \sum_{s} Y_s^{min} f_s^* \tag{C13}$$

$$FS^{min} \leq (1 - Y_s) f_s^* + Y_s f^{max} \quad \forall s \in S \tag{C14}$$

$$\sum_{s} Y_s^{min} = 1 \quad \text{(C15)}$$

$$Y_s^{min} \leq 1 - Y_s \quad \text{(C16)}$$

$$FE^{exp} \geq FS^{exp} - f^{exp} \quad \text{(C17)}$$

$$FE^{exp} \geq -FS^{exp} + f^{exp} \quad \text{(C18)}$$

$$FE^{max}=f^{max}\text{-}FS^{max} \quad \text{(C19)}$$

$$FE^{min}=FS^{min} - f^{min} \quad \text{(C20)}$$

$$\min \sum_{s} DIS_s \, p_s^{orig} + FE^{max} + FE^{min} + FE^{exp} \quad \text{(C21)}$$

Constraints (C1) – (C7) aim to the minimization of the Kantorovich distance between the initial and the reduced discrete distributions (Kantorovitch, 1958). To quantify the difference of the expected, best and worst performance of the output measures constraints (C8)- (C20) are also included. The objective function targets to minimize the Kantorovich distance and the differences of the output measures. A detailed description of the MILP scenario reduction model is also given by Li and Floudas, (2014).

`

C.2. Data of the first case study – Illustrative example

The data for the illustrative example are summarized in Tables C1 – C15

Table C1 Products to processing units mapping (kg)

Processing units	Minimum Capacity	Maximum Capacity
1	20	400
2	20	300
3	20	400
4	20	300
5	20	400
6	20	300

Table C2 Units to production stages mapping

Processing units	Processing stages		
	1	**2**	**3**
1	1	0	0
2	1	0	0
3	0	1	0
4	0	1	0
5	0	0	1
6	0	0	1

`

Table C3 Selling price of products (relative money units / kg)

Product	Selling price	Product	Selling price
1	3	**8**	3
2	1	**9**	4
3	3	**10**	4
4	4	**11**	2
5	2	**12**	2
6	4	**13**	1
7	5	**14**	5

Table C4 Backlog cost of products (relative money units / kg)

Product	Selling price	Product	Selling price
1	9	**8**	9
2	3	**9**	12
3	9	**10**	12
4	12	**11**	6
5	6	**12**	6
6	12	**13**	3
7	15	**14**	15

`

Table C5 Inventory cost of products (relative money units / kg)

Product	Selling price	Product	Selling price
1	1.5	**8**	1.5
2	0.5	**9**	2
3	1.5	**10**	2
4	2	**11**	1
5	1	**12**	1
6	2	**13**	0.5
7	2.5	**14**	2.5

Table C6 Variable raw material cost of products (relative money units / kg)

Product	Selling price	Product	Selling price
1	0.3	**8**	0.3
2	0.1	**9**	0.4
3	0.3	**10**	0.4
4	0.4	**11**	0.2
5	0.2	**12**	0.2
6	0.4	**13**	0.1
7	0.5	**14**	0.5

`

Table C7 Fixed processing time of products in each processing unit (hours)

Products	Processing units					
	1	**2**	**3**	**4**	**5**	**6**
1	1	1	1.3	1.3	1.1	1.1
2	1	1	1.3	1.3	1.1	1.1
3	1	1	1.3	1.3	1.1	1.1
4	1	1	1.3	1.3	1.1	1.1
5	1	1	1.3	1.3	1.1	1.1
6	1	1	1.3	1.3	1.1	1.1
7	1	1	1.3	1.3	1.1	1.1
8	1	1	1.3	1.3	1.1	1.1
9	1	1	1.3	1.3	1.1	1.1
10	1	1	1.3	1.3	1.1	1.1
11	1	1	1.3	1.3	1.1	1.1
12	1	1	1.3	1.3	1.1	1.1
13	1	1	1.3	1.3	1.1	1.1
14	1	1	1.3	1.3	1.1	1.1

Table C8 Variable processing time of products in each processing unit (kg/hour)

Products	Processing units					
	1	**2**	**3**	**4**	**5**	**6**
1	30	30	40	40	25	25
2	30	30	40	40	25	25
3	40	40	50	50	30	30
4	40	40	50	50	30	30
5	40	40	50	50	30	30
6	40	40	50	50	30	30
7	40	40	50	50	30	30
8	30	30	40	40	25	25
9	30	30	40	40	25	25
10	30	30	40	40	25	25
11	40	40	50	50	30	30
12	40	40	50	50	30	30
13	40	40	50	50	30	30
14	40	40	50	50	30	30

`

Table C9 Products to processing units mapping

Products	Processing units					
	1	**2**	**3**	**4**	**5**	**6**
1	1	1	1	1	1	1
2	1	1	1	1	1	1
3	0	1	0	1	0	1
4	0	1	0	1	0	1
5	1	1	1	1	1	1
6	1	1	1	1	1	1
7	1	1	1	1	1	1
8	1	0	1	0	0	1
9	1	0	1	0	0	1
10	1	0	1	0	0	1
11	1	1	1	1	1	1
12	1	1	1	1	1	1
13	1	1	1	1	1	1
14	1	1	1	1	1	1

`

Table C10 Demand of target scenario for time periods 1-10 (kg)

	week									
	1	2	3	4	5	6	7	8	9	10
1	120	120	132	132	138	120	120	132	132	138
2	120	120	132	132	138	120	120	132	132	138
3	360	360	360	396	396	360	360	360	396	396
4	156	156	172	383	372	156	156	172	383	372
5	384	384	384	383	372	384	384	384	383	372
6	384	384	384	383	372	384	384	384	383	372
7	360	360	360	396	396	360	360	360	396	396
8	360	360	360	396	396	360	360	360	396	396
9	120	120	120	132	360	120	120	120	132	360
10	384	384	384	383	372	384	384	384	383	372
11	120	120	132	132	138	120	120	132	132	138
12	120	120	132	132	138	120	120	132	132	138
13	360	360	360	396	396	360	360	360	396	396
14	180	180	180	383	372	180	180	180	383	372

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Table C11 Demand of target scenario for time periods 11-20 (kg)

	week									
	11	12	13	14	15	16	17	18	19	20
1	120	120	132	132	138	120	120	132	132	138
2	120	120	132	132	138	120	120	132	132	138
3	360	360	360	396	396	360	360	360	396	396
4	156	156	172	383	372	156	156	172	383	372
5	384	384	384	383	372	384	384	384	383	372
6	384	384	384	383	372	384	384	384	383	372
7	360	360	360	396	396	360	360	360	396	396
8	360	360	360	396	396	360	360	360	396	396
9	120	120	120	132	360	120	120	120	132	360
10	384	384	384	383	372	384	384	384	383	372
11	120	120	132	132	138	120	120	132	132	138
12	120	120	132	132	138	120	120	132	132	138
13	360	360	360	396	396	360	360	360	396	396
14	180	180	180	383	372	180	180	180	383	372

Table C12 Demand of target scenario for time periods 21-30 (kg)

	week									
	21	22	23	24	25	26	27	28	29	30
1	120	120	132	132	138	120	120	132	132	138
2	120	120	132	132	138	120	120	132	132	138
3	360	360	360	396	396	360	360	360	396	396
4	156	156	172	383	372	156	156	172	383	372
5	384	384	384	383	372	384	384	384	383	372
6	384	384	384	383	372	384	384	384	383	372
7	360	360	360	396	396	360	360	360	396	396
8	360	360	360	396	396	360	360	360	396	396
9	120	120	120	132	360	120	120	120	132	360
10	384	384	384	383	372	384	384	384	383	372
11	120	120	132	132	138	120	120	132	132	138
12	120	120	132	132	138	120	120	132	132	138
13	360	360	360	396	396	360	360	360	396	396
14	180	180	180	383	372	180	180	180	383	372
15	120	120	132	132	138	120	120	132	132	138

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Table C13 Demand of target scenario for time periods 31-40 (kg)

	week									
	31	32	33	34	35	36	37	38	39	40
1	120	120	132	132	138	120	120	132	132	138
2	120	120	132	132	138	120	120	132	132	138
3	360	360	360	396	396	360	360	360	396	396
4	156	156	172	383	372	156	156	172	383	372
5	384	384	384	383	372	384	384	384	383	372
6	384	384	384	383	372	384	384	384	383	372
7	360	360	360	396	396	360	360	360	396	396
8	360	360	360	396	396	360	360	360	396	396
9	120	120	120	132	360	120	120	120	132	360
10	384	384	384	383	372	384	384	384	383	372
11	120	120	132	132	138	120	120	132	132	138
12	120	120	132	132	138	120	120	132	132	138
13	360	360	360	396	396	360	360	360	396	396
14	180	180	180	383	372	180	180	180	383	372

Table C14 Demand of target scenario for time periods 41-52 (kg)

	week											
	41	42	43	44	45	46	47	48	49	50	51	52
1	120	120	132	132	138	120	120	132	132	138	120	120
2	120	120	132	132	138	120	120	132	132	138	120	120
3	360	360	360	396	396	360	360	360	396	396	408	408
4	156	156	172	383	372	156	156	172	383	372	311	301
5	384	384	384	383	372	384	384	384	383	311	250	250
6	384	384	384	383	372	384	384	384	383	311	250	250
7	360	360	360	396	396	360	360	360	396	311	250	250
8	360	360	360	396	396	360	360	360	396	396	360	360
9	120	120	120	132	360	120	120	120	132	360	396	436
10	384	384	384	383	372	384	384	384	383	372	311	301
11	120	120	132	132	138	120	120	132	132	138	120	120
12	120	120	132	132	138	120	120	132	132	138	120	120
13	360	360	360	396	396	360	360	360	396	396	360	360
14	180	180	180	383	372	180	180	180	383	372	311	301

Table C15 Changeover times (hours)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	0.0	1.4	1.8	1.8	1.4	1.8	1.4	1.4	1.8	1.8	1.4	1.8	1.8	1.7
2	1.4	0.0	1.8	1.8	1.4	1.8	1.4	1.4	1.8	1.8	1.4	1.8	1.8	1.7
3	1.8	1.4	0.0	1.8	1.4	1.8	1.4	1.4	1.8	1.8	1.4	1.8	1.8	1.7
4	1.8	1.4	1.8	0.0	1.4	1.8	1.4	1.4	1.8	1.8	1.4	1.8	1.8	1.7
5	1.4	1.4	1.8	1.8	0.0	1.8	1.4	1.4	1.8	1.8	1.4	1.8	1.8	1.7
6	1.8	1.4	1.8	1.8	1.4	0.0	1.4	1.4	1.8	1.8	1.4	1.8	1.8	1.7
7	1.4	1.4	1.8	1.8	1.4	1.8	0.0	1.4	1.8	1.8	1.4	1.8	1.8	1.7
8	1.5	1.4	1.8	1.8	1.4	1.8	1.4	0.0	1.8	1.8	1.4	1.8	1.8	1.7
9	1.5	1.4	1.8	1.8	1.4	1.8	1.4	1.4	0.0	1.8	1.4	1.8	1.8	1.7
10	1.5	1.4	1.8	1.8	1.4	1.8	1.4	1.4	1.8	0.0	1.4	1.8	1.8	1.7
11	1.5	1.4	1.8	1.8	1.4	1.8	1.4	1.4	1.8	1.8	0.0	1.8	1.8	1.7
12	1.5	1.4	1.8	1.8	1.4	1.8	1.4	1.4	1.8	1.8	1.4	0.0	1.8	1.7
13	1.5	1.4	1.8	1.8	1.4	1.8	1.4	1.4	1.8	1.8	1.4	1.8	0.0	1.7
14	1.5	1.4	1.8	1.8	1.4	1.8	1.4	1.4	1.8	1.8	1.4	1.8	1.8	0.0

C.3. Data of the second case study– Large-scale problem

The data for the large-scale problem instance are summarized in Tables C16 – C31

Table C16 Products to processing units mapping (kg)

Processing units	Minimum Capacity	Maximum Capacity
1	20	400
2	20	300
3	20	400
4	20	300
5	20	400
6	20	300
7	20	400

Table C17 Units to production stages mapping

Processing units	Processing stages		
	1	**2**	**3**
1	1	0	0
2	1	0	0
3	0	1	0
4	0	1	0
5	0	0	1
6	0	0	1
7	0	0	1

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Table C18 Selling price of products (relative monetary units / kg)

Product	Selling price	Product	Selling price
1	8	**16**	8
2	4	**17**	12
3	8	**18**	14
4	7	**19**	12
5	8	**20**	11.4
6	6.2	**21**	10.8
7	7.2	**22**	11.2
8	5.6	**23**	7.8
9	5.2	**24**	16
10	4.8	**25**	18
11	12	**26**	16
12	6	**27**	17
13	7	**28**	16
14	7	**29**	19
15	12	**30**	22

Table C19 Backlog cost of products (relative money units / kg)

Product	Selling price	Product	Selling price
1	24	**16**	0.8
2	12	**17**	0.4
3	24	**18**	0.8
4	21	**19**	0.7
5	24	**20**	0.8
6	18.6	**21**	0.62
7	21.6	**22**	0.72

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8	16.8	**23**	0.56
9	15.6	**24**	0.52
10	14.4	**25**	0.48
11	36	**26**	1.2
12	18	**27**	0.6
13	21	**28**	0.7
14	21	**29**	0.7
15	36	**30**	1.2

Table C20 Inventory cost of products (relative money units / kg)

Product	Selling price	Product	Selling price
1	4	**16**	4
2	2	**17**	6
3	4	**18**	7
4	3.5	**19**	6
5	4	**20**	5.7
6	3.1	**21**	5.4
7	3.6	**22**	5.6
8	2.8	**23**	3.9
9	2.6	**24**	8
10	2.4	**25**	9
11	6	**26**	8
12	3	**27**	8.5
13	3.5	**28**	8
14	3.5	**29**	9.5
15	6	**30**	11

Table C21 Variable raw material cost of products (relative money units / kg)

Product	Selling price	Product	Selling price
1	0.8	**16**	0.8
2	0.4	**17**	1.2
3	0.8	**18**	1.4
4	0.7	**19**	1.2
5	0.8	**20**	1.14
6	0.62	**21**	1.08
7	0.72	**22**	1.12
8	0.56	**23**	0.78
9	0.52	**24**	1.6
10	0.48	**25**	1.8
11	1.2	**26**	1.6
12	0.6	**27**	1.7
13	0.7	**28**	1.6
14	0.7	**29**	1.9
15	1.2	**30**	2.2

Table C22 Fixed processing time of products in each processing unit (hours)

Products	Processing units						
	1	2	3	4	5	6	7
1	1	1	1.3	1.3	1.1	1.1	0.2
2	1	1	1.3	1.3	1.1	1.1	0.2
3	1	1	1.3	1.3	1.1	1.1	0.2
4	1	1	1.3	1.3	1.1	1.1	0.2
5	1	1	1.3	1.3	1.1	1.1	0.2
6	1	1	1.3	1.3	1.1	1.1	0.2

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7	1	1	1.3	1.3	1.1	1.1	0.2
8	1	1	1.3	1.3	1.1	1.1	0.2
9	1	1	1.3	1.3	1.1	1.1	0.2
10	1	1	1.3	1.3	1.1	1.1	0.2
11	1	1	1.3	1.3	1.1	1.1	0.2
12	1	1	1.3	1.3	1.1	1.1	0.2
13	1	1	1.3	1.3	1.1	1.1	0.2
14	1	1	1.3	1.3	1.1	1.1	0.2
15	1	1	1.3	1.3	1.1	1.1	0.2
16	1	1	1.3	1.3	1.1	1.1	0.2
17	1	1	1.3	1.3	1.1	1.1	0.2
18	1	1	1.3	1.3	1.1	1.1	0.2
19	1	1	1.3	1.3	1.1	1.1	0.2
20	1	1	1.3	1.3	1.1	1.1	0.2
21	1	1	1.3	1.3	1.1	1.1	0.2
22	1	1	1.3	1.3	1.1	1.1	0.2
23	1	1	1.3	1.3	1.1	1.1	0.2
24	1	1	1.3	1.3	1.1	1.1	0.2
25	1	1	1.3	1.3	1.1	1.1	0.2
26	1	1	1.3	1.3	1.1	1.1	0.2
27	1	1	1.3	1.3	1.1	1.1	0.2
28	1	1	1.3	1.3	1.1	1.1	0.2
29	1	1	1.3	1.3	1.1	1.1	0.2
30	1	1	1.3	1.3	1.1	1.1	0.2

Table C23 Variable processing time of products in each processing unit (kg/hour)

Products	**Processing units**						
	1	**2**	**3**	**4**	**5**	**6**	**7**
1	30	30	40	40	25	25	25
2	30	30	40	40	25	25	25
3	40	40	50	50	30	30	30
4	40	40	50	50	30	30	30
5	40	40	50	50	30	30	30
6	40	40	50	50	30	30	30
7	40	40	50	50	30	30	30
8	30	30	40	40	25	25	25
9	30	30	40	40	25	25	25
10	30	30	40	40	25	25	25
11	40	40	50	50	30	30	30
12	40	40	50	50	30	30	30
13	40	40	50	50	30	30	30
14	40	40	50	50	30	30	30
15	40	40	50	50	30	30	30
16	40	40	50	50	30	30	30
17	40	40	50	50	30	30	30
18	30	30	40	40	25	25	25
19	30	30	40	40	25	25	25
20	30	30	40	40	25	25	25
21	30	30	40	40	25	25	25
22	30	30	40	40	25	25	25
23	30	30	40	40	25	25	25
24	40	40	50	50	30	30	30
25	40	40	50	50	30	30	30

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26	40	40	50	50	30	30	30
27	40	40	50	50	30	30	30
28	40	40	50	50	30	30	30
29	30	30	40	40	25	25	25
30	30	30	40	40	25	25	25

Table C24 Products to processing units mapping

Products	**Processing units**						
	1	**2**	**3**	**4**	**5**	**6**	**7**
1	1	1	1	1	1	1	1
2	1	1	1	1	1	1	1
3	0	1	0	1	0	1	1
4	0	1	0	1	0	1	1
5	1	1	1	1	1	1	1
6	1	1	1	1	1	1	1
7	1	1	1	1	1	1	1
8	1	0	1	0	0	1	1
9	1	0	1	0	0	1	1
10	1	0	1	0	0	1	1
11	1	1	1	1	1	1	1
12	1	1	1	1	1	1	1
13	1	1	1	1	1	1	1
14	1	1	1	1	1	1	1
15	0	1	0	1	0	1	1
16	0	1	0	1	0	1	1
17	0	1	0	1	0	1	1
18	1	0	1	0	1	0	1

19	1	0	1	0	1	0	1
20	1	0	1	0	1	0	1
21	0	1	0	1	0	1	1
22	0	1	0	1	0	1	1
23	0	1	0	1	0	1	1
24	0	1	0	1	0	1	1
25	0	1	0	1	0	1	1
26	0	1	0	1	0	1	1
27	1	1	1	1	1	1	1
28	1	1	1	1	1	1	1
29	1	1	1	1	1	1	1
30	1	1	1	1	1	1	1

Table C25 Demand of target scenario for time periods 1-10 (kg)

	week									
	1	2	3	4	5	6	7	8	9	10
1	120	120	132	132	138	120	120	132	132	138
2	120	120	132	132	138	120	120	132	132	138
3	360	360	360	396	396	360	360	360	396	396
4	156	156	171.6	382.93	372	156	156	171.6	382.9	372
5	384	384	384	382.93	372	384	384	384	382.9	372
6	384	384	384	382.93	372	384	384	384	382.9	372
7	360	360	360	396	396	360	360	360	396	396
8	360	360	360	396	396	360	360	360	396	396
9	120	120	120	132	360	120	120	120	132	360
10	384	384	384	382.9	372	384	384	384	382.9	372

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11	345	345	345	381	381	345	345	345	381	381
12	170	170	185.6	396.9	386	170	170	185.6	396.9	386
13	360	360	360	396	396	360	360	360	396	396
14	180	180	180	382.9	372	180	180	180	382.9	372
15	384	384	384	382.9	372	384	384	384	382.9	372
16	384	384	384	382.9	372	384	384	384	382.9	372
17	360	360	360	396	396	360	360	360	396	396
18	384	384	384	382.9	372	362.	351.9	362.4	331.	321.1
19	132	132	145.2	382.93	372	362.	351.91	341.64	331.38	321.1
20	360	360	360	396	396	396	435.6	360	360	360
21	384	384	384	382.93	372	362.	351.91	341.6	331.3	321.1
22	264	264	290.4	316.8	316	343	396	448.8	408	408
23	240	240	264	288	288	312	360	408	408	408
24	120	120	132	144	360	360	360	360	228	240
25	132	132	145.2	158.4	158	171	198	224.4	250.8	264
26	384	384	384	382.93	372	362	351.9	341.6	331.38	321.11
27	240	240	264	288	288	312	360	408	408	408
28	264	264	290.4	316.8	316.8	343.2	396	448.8	408	408
29	360	360	360	396	396	360	360	360	396	396
30	156	156	171.6	382.93	372	156	156	171.6	382.93	372

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Table C26 Demand of target scenario for time periods 11-20 (kg)

	week									
	11	12	13	14	15	16	17	18	19	20
1	120	120	132	132	138	120	120	132	132	138
2	120	120	132	132	138	120	120	132	132	138
3	360	360	360	396	396	360	360	360	396	396
4	156	156	171.6	382.93	372	156	156	171.6	382.9	372
5	384	384	384	382.98	372	384	384	384	382.9	372
6	384	384	384	382.98	372	384	384	384	382.93	372
7	360	360	360	396	396	360	360	360	396	396
8	360	360	360	396	396	360	360	360	396	396
9	120	120	120	132	360	120	120	120	132	360
10	384	384	384	382.93	372	384	384	384	382.931	372
11	345	345	345	381	381	345	345	345	381	381
12	170	170	185.6	396.9	386	170	170	185.6	396.91	386
13	360	360	360	396	396	360	360	360	396	396
14	180	180	180	382.93	372	180	180	180	382.93	372
15	384	384	384	382.93	372	384	384	384	382.93	372
16	384	384	384	382.93	372	384	384	384	382.93	372
17	360	360	360	396	396	360	360	360	396	396
18	310.8	300.58	290.3	280.0	269.78	384	384	384	382.93	312
19	310.4	300.5	382.93	372	362.4	351.9	341. 8	331.3	382.9	382.9
20	360	360	396	396	396	360	360	360	396	312
21	310.8	300.5	290.3	280.05	269.78	384	384	384	382.93	408
22	408	408	408	408	408	408	408	408	408	408
23	408	408	408	408	408	408	408	408	408	408
24	264	300	306	312	312	312	312	312	312	312
25	290.4	330	336.6	343.2	343.2	343.2	343.2	343.2	343.2	343.2

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26	310.8	300.5	290.35	280.05	269. 4	384	384	384	382.9	312
27	408	408	408	408	408	408	408	408	408	408
28	408	408	408	408	408	408	408	408	408	408
29	360	360	360	396	396	360	360	360	396	396
30	156	156	171.6	382.9	372	156	156	171.6	382.93	372

Table C27 Demand of target scenario for time periods 21-30 (kg)

	week									
	21	22	23	24	25	26	27	28	29	30
1	120.0	120.0	132.0	132.0	138.0	120.0	120.0	132.0	132.0	138.0
2	120.0	120.0	132.0	132.0	138.0	120.0	120.0	132.0	132.0	138.0
3	360.0	360.0	360.0	396.0	396.0	360.0	360.0	360.0	396.0	396.0
4	156.0	156.0	171.6	382.9	372.0	156.0	156.0	171.6	382.9	372.0
5	384.0	384.0	384.0	382.9	372.0	384.0	384.0	384.0	382.9	372.0
6	384.0	384.0	384.0	382.9	372.0	384.0	384.0	384.0	382.9	372.0
7	360.0	360.0	360.0	396.0	396.0	360.0	360.0	360.0	396.0	396.0
8	360.0	360.0	360.0	396.0	396.0	360.0	360.0	360.0	396.0	396.0
9	120.0	120.0	120.0	132.0	360.0	120.0	120.0	120.0	132.0	360.0
10	384.0	384.0	384.0	382.9	372.0	384.0	384.0	384.0	382.9	372.0
11	345.0	345.0	345.0	381.0	381.0	345.0	345.0	345.0	381.0	381.0
12	170.0	170.0	185.6	396.9	386.0	170.0	170.0	185.6	396.9	386.0
13	360.0	360.0	360.0	396.0	396.0	360.0	360.0	360.0	396.0	396.0
14	180.0	180.0	180.0	382.9	372.0	180.0	180.0	180.0	382.9	372.0
15	384.0	384.0	384.0	382.9	372.0	384.0	384.0	384.0	382.9	372.0
16	384.0	384.0	384.0	382.9	372.0	384.0	384.0	384.0	382.9	372.0
17	360.0	360.0	360.0	396.0	396.0	360.0	360.0	360.0	396.0	396.0
18	312.0	312.0	312.0	312.0	312.0	312.0	312.0	312.0	312.0	312.0
19	343.2	343.2	343.2	343.2	343.2	343.2	343.2	343.2	343.2	343.2

20	312.0	312.0	312.0	312.0	312.0	312.0	312.0	312.0	312.0	312.0
21	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0
22	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0
23	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0
24	312.0	312.0	312.0	312.0	312.0	312.0	312.0	312.0	312.0	312.0
25	343.2	343.2	343.2	343.2	343.2	343.2	343.2	343.2	343.2	343.2
26	312.0	312.0	312.0	312.0	312.0	312.0	312.0	312.0	312.0	312.0
27	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0
28	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0
29	360.0	360.0	360.0	396.0	396.0	360.0	360.0	360.0	396.0	396.0
30	156.0	156.0	171.6	382.9	372.0	156.0	156.0	171.6	382.9	372.0

Table C28 Demand of target scenario for time periods 31-40 (kg)

	week									
	31	32	33	34	35	36	37	38	39	40
1	120.0	120.0	132.0	132.0	138.0	120.0	120.0	132.0	132.0	138.0
2	120.0	120.0	132.0	132.0	138.0	120.0	120.0	132.0	132.0	138.0
3	360.0	360.0	360.0	396.0	396.0	360.0	360.0	360.0	396.0	396.0
4	156.0	156.0	171.6	382.9	372.0	156.0	156.0	171.6	382.9	372.0
5	384.0	384.0	384.0	382.9	372.0	384.0	384.0	384.0	382.9	372.0
6	384.0	384.0	384.0	382.9	372.0	384.0	384.0	384.0	382.9	372.0
7	360.0	360.0	360.0	396.0	396.0	360.0	360.0	360.0	396.0	396.0
8	360.0	360.0	360.0	396.0	396.0	360.0	360.0	360.0	396.0	396.0
9	120.0	120.0	120.0	132.0	360.0	120.0	120.0	120.0	132.0	360.0
10	384.0	384.0	384.0	382.9	372.0	384.0	384.0	384.0	382.9	372.0
11	345.0	345.0	345.0	381.0	381.0	345.0	345.0	345.0	381.0	381.0
12	170.0	170.0	185.6	396.9	386.0	170.0	170.0	185.6	396.9	386.0
13	360.0	360.0	360.0	396.0	396.0	360.0	360.0	360.0	396.0	396.0

14	180.0	180.0	180.0	382.9	372.0	180.0	180.0	180.0	382.9	372.0
15	384.0	384.0	384.0	382.9	372.0	384.0	384.0	384.0	382.9	372.0
16	384.0	384.0	384.0	382.9	372.0	384.0	384.0	384.0	382.9	372.0
17	360.0	360.0	360.0	396.0	396.0	360.0	360.0	360.0	396.0	396.0
18	312.0	312.0	312.0	312.0	312.0	312.0	312.0	312.0	312.0	312.0
19	343.2	343.2	343.2	343.2	343.2	343.2	343.2	343.2	343.2	343.2
20	312.0	312.0	312.0	312.0	312.0	312.0	312.0	312.0	312.0	312.0
21	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0
22	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0
23	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0
24	312.0	312.0	312.0	312.0	312.0	312.0	312.0	312.0	312.0	312.0
25	343.2	343.2	343.2	343.2	343.2	343.2	343.2	343.2	343.2	343.2
26	312.0	312.0	312.0	312.0	312.0	312.0	312.0	312.0	312.0	312.0
27	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0
28	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0	408.0
29	360	360	360	396	396	360	360	360	396	396
30	156	156	171.6	382.9	372	156	156	171.6	382.9	372

Table C29 Demand of target scenario for time periods 41-52 (kg)

	week											
	41	42	43	44	45	46	47	48	49	50	51	52
1	120	120	132	132	138	120	120	132	132	138	120	120
2	120	120	132	132	138	120	120	132	132	138	120	120
3	360	360	360	396	396	360	360	360	396	396	408	408
4	156	156	171.6	382.9	372	156	156	171.6	382.9	372	310.8	300.6
5	384	384	384	382.9	372	384	384	384	382.9	310.8	249.7	249.7
6	384	384	384	382.9	372	384	384	384	382.9	310.8	249.7	249.7
7	360	360	360	396	396	360	360	360	396	310.8	249.7	249.7

8	360	360	360	396	396	360	360	360	396	396	360	360
9	120	120	120	132	360	120	120	120	132	360	396	435.6
10	384	384	384	382.9	372	384	384	384	382.9	372	310.8	300.6
11	345	345	345	381	381	345	345	345	381	381	393	393
12	170	170	185.6	396.9	386	170	170	185.6	396.9	386	324.8	314.6
13	360	360	360	396	396	360	360	360	396	396	360	360
14	180	180	180	382.9	372	180	180	180	382.9	372	310.8	300.6
15	384	384	384	382.9	372	384	384	384	382.9	310.8	249.7	249.7
16	384	384	384	382.9	372	384	384	384	382.9	310.8	249.7	249.7
17	360	360	360	396	396	360	360	360	396	310.8	249.7	249.7
18	312	312	312	312	312	312	312	312	312	312	312	312
19	343.2	343.2	343.2	343.2	343.2	343.2	343.2	343.2	343.2	343.2	343.2	343.2
20	312	312	312	312	312	312	312	312	312	312	312	312
21	360	360	360	360	336	336	336	336	336	336	336	336
22	360	360	360	360	336	336	336	336	336	336	336	336
23	360	360	360	360	336	336	336	336	336	336	336	336
24	312	312	312	312	312	312	312	312	312	312	312	312
25	343.2	343.2	343.2	343.2	343.2	343.2	343.2	343.2	343.2	343.2	343.2	343.2
26	312	312	312	312	312	312	312	312	312	312	312	312
27	360	360	360	360	336	336	336	336	336	336	336	336
28	360	360	360	360	336	336	336	336	336	336	336	336
29	360	360	360	396	396	360	360	360	396	396	408	408
30	156	156	171.6	382.9	372	156	156	171.6	382.9	372	310.8	300.6

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Table C30 Changeover times between products (hours)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	0.0	1.4	1.8	1.8	1.4	1.8	1.4	1.4	1.8	1.8	1.4	1.8	1.8	1.7	1.7
2	1.4	0.0	1.8	1.8	1.4	1.8	1.4	1.4	1.8	1.8	1.4	1.8	1.8	1.7	1.7
3	1.8	1.4	0.0	1.8	1.4	1.8	1.4	1.4	1.8	1.8	1.4	1.8	1.8	1.7	1.7
4	1.8	1.4	1.8	0.0	1.4	1.8	1.4	1.4	1.8	1.8	1.4	1.8	1.8	1.7	1.7
5	1.4	1.4	1.8	1.8	0.0	1.8	1.4	1.4	1.8	1.8	1.4	1.8	1.8	1.7	1.7
6	1.8	1.4	1.8	1.8	1.4	0.0	1.4	1.4	1.8	1.8	1.4	1.8	1.8	1.7	1.7
7	1.4	1.4	1.8	1.8	1.4	1.8	0.0	1.4	1.8	1.8	1.4	1.8	1.8	1.7	1.7
8	1.5	1.4	1.8	1.8	1.4	1.8	1.4	0.0	1.8	1.8	1.4	1.8	1.8	1.7	1.7
9	1.5	1.4	1.8	1.8	1.4	1.8	1.4	1.4	0.0	1.8	1.4	1.8	1.8	1.7	1.7
10	1.5	1.4	1.8	1.8	1.4	1.8	1.4	1.4	1.8	0.0	1.4	1.8	1.8	1.7	1.7
11	1.5	1.4	1.8	1.8	1.4	1.8	1.4	1.4	1.8	1.8	0.0	1.8	1.8	1.7	1.7
12	1.5	1.4	1.8	1.8	1.4	1.8	1.4	1.4	1.8	1.8	1.4	0.0	1.8	1.7	1.7
13	1.5	1.4	1.8	1.8	1.4	1.8	1.4	1.4	1.8	1.8	1.4	1.8	0.0	1.7	1.7
14	1.5	1.4	1.8	1.8	1.4	1.8	1.4	1.4	1.8	1.8	1.4	1.8	1.8	0.0	1.7
15	1.4	1.4	1.8	1.8	1.4	1.8	1.4	1.4	1.8	1.8	1.4	1.8	1.8	1.7	0.0
16	1.4	1.4	1.8	1.8	1.4	1.8	1.4	1.4	1.8	1.8	1.4	1.8	1.8	1.8	1.8
17	1.4	1.4	1.8	1.8	1.4	1.8	1.4	1.4	1.8	1.8	1.4	1.8	1.8	1.8	1.8
18	1.4	1.4	1.8	1.8	1.4	1.8	1.4	1.4	1.8	1.8	1.4	1.8	1.8	1.8	1.8
19	1.4	1.4	1.8	1.8	1.4	1.8	1.4	1.4	1.8	1.8	1.4	1.8	1.8	1.8	1.8
20	1.4	1.8	1.8	1.4	1.8	1.4	1.4	1.8	1.8	1.4	1.8	1.8	1.8	1.8	1.8
21	1.5	1.6	1.9	1.8	1.5	1.7	1.4	1.4	1.8	1.6	1.4	1.7	1.6	1.6	1.6
22	1.5	1.6	1.9	1.8	1.5	1.8	1.4	1.4	1.8	1.6	1.4	1.7	1.6	1.6	1.6
23	1.5	1.6	2.0	1.8	1.5	1.8	1.4	1.4	1.8	1.6	1.4	1.7	1.6	1.6	1.6
24	1.5	1.6	2.0	1.8	1.5	1.8	1.4	1.5	1.8	1.6	1.4	1.7	1.6	1.6	1.6
25	1.6	1.6	2.0	1.8	1.6	1.8	1.4	1.5	1.8	1.6	1.4	1.7	1.6	1.6	1.6
26	1.6	1.7	2.0	1.9	1.6	1.8	1.4	1.5	1.8	1.6	1.4	1.6	1.6	1.6	1.5

27	1.6	1.7	2.0	1.9	1.6	1.8	1.4	1.5	1.8	1.6	1.4	1.6	1.6	1.6	1.5
28	1.6	1.7	2.1	1.9	1.6	1.8	1.4	1.5	1.8	1.6	1.4	1.6	1.6	1.6	1.5
29	1.6	1.7	2.1	1.9	1.6	1.8	1.4	1.5	1.8	1.6	1.4	1.6	1.6	1.6	1.5
30	1.6	1.8	2.1	1.9	1.6	1.8	1.4	1.5	1.8	1.6	1.4	1.6	1.6	1.6	1.5

Table C31 Changeover times between products (hours)

	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
1	1.8	1.4	1.8	1.8	1.4	1.8	1.9	1.9	1.9	1.9	2.0	2.0	2.0	2.0	2.1
2	1.4	1.4	1.8	1.8	1.4	1.7	1.8	1.8	1.8	1.8	1.9	1.9	1.9	1.9	1.9
3	1.8	1.4	1.8	1.8	1.4	1.8	1.8	1.8	1.8	1.9	1.9	1.9	1.9	1.9	2.0
4	1.4	1.4	1.8	1.8	1.4	1.7	1.7	1.7	1.7	1.7	1.8	1.8	1.8	1.8	1.8
5	1.5	1.4	1.8	1.8	1.4	1.7	1.7	1.7	1.8	1.8	1.8	1.8	1.8	1.8	1.9
6	1.5	1.4	1.8	1.8	1.4	1.6	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7
7	1.5	1.4	1.8	1.8	1.4	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.8	1.8
8	1.5	1.4	1.8	1.8	1.4	1.6	1.6	1.6	1.6	1.6	1.7	1.7	1.7	1.7	1.7
9	1.5	1.4	1.8	1.8	1.4	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6
10	1.5	1.4	1.8	1.8	1.4	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6
11	1.5	1.4	1.8	1.8	1.4	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6
12	1.4	1.4	1.8	1.8	1.4	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
13	1.4	1.4	1.8	1.8	1.4	1.5	1.5	1.5	1.5	1.5	1.5	1.4	1.4	1.4	1.4
14	1.4	1.4	1.8	1.8	1.4	1.5	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4
15	1.4	1.4	1.8	1.8	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4
16	0.0	1.4	1.8	1.8	1.4	1.5	1.5	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4
17	1.4	0.0	1.8	1.8	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4
18	1.8	1.4	0.0	1.8	1.4	1.4	1.4	1.4	1.4	1.4	1.3	1.3	1.3	1.3	1.3
19	1.8	1.4	1.8	0.0	1.4	1.4	1.4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.2
20	1.4	1.4	1.8	1.8	0.0	1.4	1.4	1.3	1.3	1.3	1.3	1.3	1.3	1.2	1.2

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21	1.3	1.1	1.5	1.5	1.1	0.0	1.3	1.3	1.3	1.2	1.2	1.2	1.2	1.2	1.1
22	1.3	1.1	1.5	1.4	1.1	1.3	0.0	1.3	1.2	1.2	1.2	1.2	1.1	1.1	1.1
23	1.3	1.1	1.5	1.4	1.0	1.3	1.2	0.0	1.2	1.2	1.2	1.1	1.1	1.1	1.1
24	1.2	1.1	1.4	1.4	1.0	1.3	1.2	1.2	0.0	1.1	1.1	1.1	1.1	1.0	1.0
25	1.2	1.1	1.4	1.4	1.0	1.2	1.2	1.2	1.1	0.0	1.1	1.1	1.0	1.0	1.0
26	1.2	1.1	1.4	1.4	1.0	1.2	1.2	1.1	1.1	1.1	0.0	1.0	1.0	1.0	0.9
27	1.2	1.1	1.4	1.3	1.0	1.2	1.1	1.1	1.1	1.0	1.0	0.0	1.0	0.9	0.9
28	1.2	1.1	1.4	1.3	0.9	1.2	1.1	1.1	1.1	1.0	1.0	0.9	0.0	0.9	0.8
29	1.2	1.0	1.3	1.3	0.9	1.1	1.1	1.1	1.0	1.0	0.9	0.9	0.9	0.0	0.8
30	1.2	1.0	1.3	1.3	0.9	1.1	1.1	1.0	1.0	1.0	0.9	0.9	0.8	0.8	0.0

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C4. Results for the second case study– Initial and new plant layout

Table C32 Summary of results for all contract combinations (initial plant layout)

Feasible Contact combination	Exp. Profit	$VaR_{90\%}$	$VaR_{95\%}$	$CVaR_{90\%}$	$CVaR_{95\%}$	Max. Profit
C1-C7-C8	8.10	6.03	4.34	4.58	3.98	12.64
C1-C2-C5-C11	8.01	5.08	5.08	4.89	4.70	11.73
C1-C2-C5-C12	7.74	5.50	5.50	5.12	4.74	11.75
C1-C2-C6-C11	7.57	4.55	4.55	4.43	4.31	11.11
C1-C5-C6-C11	7.51	5.05	5.05	4.90	4.74	10.55
C1-C8-C12	7.28	3.64	3.64	3.43	3.23	12.98
C1-C7-C12	7.18	3.96	3.96	3.77	3.59	12.96
C1-C3-C7	7.08	4.36	4.36	4.33	4.30	8.24
C1-C3-C12	7.04	4.40	4.40	4.11	3.82	10.77
C1-C5-C11	6.91	3.61	3.61	3.46	3.30	10.07
C1-C5-C12	6.61	3.62	3.62	3.62	3.62	10.23
C1-C2-C11	6.25	3.13	3.13	2.98	2.83	10.12
C1-C6-C11	6.14	3	3	2.88	2.75	9.54
C1-C2-C12	5.98	3.14	2.64	2.91	2.69	10.24
C1-C6-C12	5.89	3.01	3.01	2.82	2.64	9.69
C1-C6-C8	5.87	2.99	2.97	2.93	2.89	8.12
C1-C2-C7	5.85	3.10	3.10	3.07	3.05	7.58
C1-C6-C7	5.79	2.97	2.97	2.95	2.93	7.12
C1-C2-C5-C6	5.66	4.30	4.30	4.30	4.30	6.46
C1-C5-C16	5.30	3.13	3.13	2.88	2.64	9.36
C1-C11	4.76	1.25	1.25	1.22	1.19	8.16
C1-C8	4.52	1.24	1.24	1.23	1.22	6.72
C1-C12	4.49	1.26	1.16	1.21	1.16	8.28
C1-C7	4.18	1.22	1.22	1.21	1.21	5.60
C1-C2-C5	4.17	3.26	3.26	3.26	3.26	4.83

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C1-C3-C5	4.10	2.83	2.83	2.83	2.83	4.82
C1-C2-C6	3.61	2.45	2.45	2.45	2.45	4.33
C1-C3-C6	3.60	2.71	2.71	2.71	2.71	4.13
C1-C3	3.25	2.60	2.60	2.60	2.60	3.90
C1-C5	2.57	2.06	2.06	2.06	2.06	3.09
C1-C2	2.15	1.72	1.72	1.72	1.72	2.58
C1-C6	2.04	1.63	1.63	1.63	1.63	2.45

**The values represent millions of relative monetary units (r.m.u.)*

Table C33 Summary of results for all contract combinations (new plant layout)

Feasible Contact combination	**Exp. Profit**	**$VaR_{90\%}$**	**$VaR_{95\%}$**	**$CVaR_{90\%}$**	**$CVaR_{95\%}$**	**Max. Profit**
C1-C6-C7-C11	9.31	5.70	5.70	5.52	5.34	13.74
C1-C7-C8	8.12	6.03	4.34	5.64	4.09	12.64
C1-C2-C5-C11	8.01	5.08	5.08	4.89	4.70	11.73
C1-C7-C11	7.85	3.95	3.95	3.78	3.61	12.93
C1-C2-C5-C12	7.74	5.50	5.50	5.12	4.74	11.75
C1-C2-C6-C11	7.57	4.55	4.55	4.43	4.31	11.11
C1-C5-C6-C11	7.51	5.05	5.05	4.90	4.74	10.55
C1-C8-C12	7.39	3.64	3.64	3.43	3.23	14.34
C1-C8-C11	7.38	3.64	3.64	3.43	3.23	13.04
C1-C7-C12	7.20	3.96	3.96	3.77	3.59	13.27
C1-C5-C6-C8	7.17	5.35	5.35	4.97	4.92	9.21
C1-C3-C7	7.08	4.36	4.36	4.33	4.30	8.86
C1-C3-C12	7.04	4.40	4.40	4.11	3.82	10.77
C1-C5-C11	6.91	3.61	3.61	3.46	3.30	10.07
C1-C5-C12	6.61	3.62	3.62	3.62	3.62	10.23
C1-C2-C11	6.25	3.13	3.13	2.98	2.83	10.12
C1-C4-C11	6.21	3.12	3.12	2.99	2.86	9.44

C1-C6-C11	6.14	3	3	2.88	2.75	9.54
C1-C5-C8	6.12	3.12	3.12	3.07	3.03	8.56
C1-C2-C12	5.98	3.14	3.14	2.91	2.69	10.24
C1-C6-C12	5.89	3.01	3.01	2.82	2.64	9.69
C1-C6-C8	5.87	2.99	2.99	2.93	2.89	8.12
C1-C2-C7	5.85	3.10	3.10	3.07	3.05	7.58
C1-C6-C7	5.79	2.97	2.97	2.95	2.93	7.12
C1-C2-C5-C6	5.71	4.46	4.46	4.46	4.46	6.87
C1-C4-C12	5.30	3.13	3.13	2.88	2.64	9.36
C1-C3-C5	5.29	4.24	4.24	4.24	4.24	6.27
C1-C2-C3	4.85	3.64	3.64	3.64	3.64	5.79
C1-C12	4.76	1.25	1.25	1.22	1.19	8.16
C1-C8	4.52	1.24	1.24	1.23	1.22	6.72
C1-C11	4.52	1.24	1.24	1.23	1.22	6.72
C1-C2-C5	4.20	3.26	3.26	3.26	3.26	5.05
C1-C7	4.18	1.22	1.22	1.21	1.21	5.60
C1-C4-C5	4.17	3.15	3.15	3.15	3.15	4.89
C1-C2-C4	3.67	2.39	2.39	2.39	2.39	4.31
C1-C2-C6	3.66	2.91	2.91	2.91	2.91	4.40
C1-C4	3.65	2.84	2.84	2.84	2.84	4.33
C1-C3	3.25	2.60	2.60	2.60	2.60	3.90
C1-C5	2.57	2.06	2.06	2.06	2.06	3.09
C1-C2	2.15	1.72	1.72	1.72	1.72	2.58
C1-C6	2.04	1.63	1.63	1.63	1.63	2.45

**The values represent millions of relative monetary units (r.m.u.)*

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