ARISTOTLE UNIVERSITY OF THESSALONIKI

Optimal Production Planning and Scheduling of Mixed Batch and Continuous Industrial Processes

By

Georgios P. Georgiadis

A Thesis

Submitted in Partial Fulfilment of the Requirements

for the Degree of Doctor of Philosophy in the

Department of Chemical Engineering

July 2021

Declaration of Authorship

I, Georgios Georgiadis, declare that this thesis titled, “Optimal production planning and scheduling of mixed batch and continuous industrial 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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Examination Committee Members

Michael C. Georgiadis
Professor
Supervisor
Dept. of Chemical Engineering
Aristotle University of Thessaloniki

Dimitrios Vlachos
Professor
Advisory Committee Member
Dept. of Mechanical Engineering
Aristotle University of Thessaloniki

Spyridon Voutetakis
Advisory Committee Member
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Centre for Research and Technology Hellas

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International Hellenic University

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Examiner
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University of Western Macedonia

Patroklos Vareltzis
Assistant Professor
Examiner
Dept. of Chemical Engineering
Aristotle University of Thessaloniki

σε αυτούς που πλημμυρίζουν τη ζωή μου αγάπη

μπαμπά, μαμά, Έλενα

σε εσάς

ARISTOTLE UNIVERSITY OF THESSALONIKI

Abstract

Faculty of Engineering
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Doctor of Philosophy

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The use of techniques for the optimization of decision-making procedures in the process industries (chemicals, food, pharmaceuticals, pulp and paper, oil and gas, cement, etc.) is more relevant than ever. Current markets are characterised by increased competitiveness that forces process industries to operate with miniscule profit margins. Therefore, improved production and resource efficiency is critical for the viability and future growth of all industries. Moreover, the European Union has identified energy and resource efficiency as a key milestone on the path towards a sustainable circular economy. Consolidated targets on this path for 2030 are:

- a 40% cut in greenhouse gas emissions compared to 1990 levels,
- a 27% to 30% share of renewable energy consumption and
- 27% to 30% energy savings compared with the business-as-usual scenario.

These targets can be achieved not only by technical innovations and new plants, but also with the introduction of computer-aided optimization technique tools and methodologies. Production planning and scheduling is the process related to the efficient allocation of resources, such as equipment, utilities and manpower, over a given time horizon of interest, e.g., daily, weekly etc., so that all required tasks are executed, and incoming orders are satisfied. Efficient production planning and scheduling is extremely beneficial to all industries, since some of the induced benefits are increased productivity, lower production costs and reduced energy needs and waste. Despite the increased use

of digitalization, production planning and scheduling remains a manual process mainly due to the lack of optimized methods that can handle real-life problems.

This thesis considers the development of mathematical frameworks to provide optimized solutions for a wide range of high complexity production planning and scheduling problems. The proposed methodologies are based on mixed integer linear programming (MILP) modelling frameworks. A known issue of this modelling technique is that the model size increases exponentially with the problem size. As a result, large-scale problems become easily intractable. Therefore, several novel solution algorithms have been investigated to allow the applicability of the presented methodologies in real-life industrial problems. The proposed solution strategies can address large-scale problems using commercially available MILP solvers, such as CPLEX and GUROBI.

More specifically, the first chapters consider the production scheduling problem of multiproduct plants comprising of mixed batch and continuous processes, a layout commonly met in several industrial sectors, such as food, pharmaceuticals, specialty chemicals etc. First, two MILP-based mathematical frameworks with distinct advantages are presented for the optimal production scheduling problem of such industrial facilities. The developed frameworks are then successfully applied on a real-life scheduling problem of a food industry. Near-optimal solutions are efficiently generated, comparing favourably with manually derived schedules by the production engineers.

Next, an optimization-based solution strategy is proposed for the integrated production planning and scheduling problem in breweries. Beer production consists of multiple batch and continuous processing steps, but it is also characterized by a long lead time, making the efficient coordination of production a difficult task. An extensive computational analysis shows the superiority of the developed methodology compared to other approaches in the open literature, while a problem originating from a real Greek brewery is used to illustrate the applicability of the proposed framework.

The optimal planning of COVID-19 vaccine supply chains is addressed in the final part of this thesis. A novel MILP model is developed to generate optimal tactical and operational decisions for the underlying supply chain problem. Key issues of the COVID-19 vaccine supply chain e.g., vaccination targets, transportation lead-times and vaccine perishability, are cleverly incorporated in the model to optimise an economic objective.

Furthermore, a decomposition strategy is introduced to address realistically sized case studies and applied to a case simulating the Greek COVID-19 vaccination program. Finally, a rolling-horizon technique is introduced to address uncertainty factors such as demand fluctuations due to cancelled vaccination appointments.

Περίληψη

Το ερευνητικό έργο που παρουσιάζεται σε αυτή τη διδακτορική διατριβή πραγματεύεται την ανάπτυξη μαθηματικών μοντέλων μεικτού ακέραιου γραμμικού προγραμματισμού (MILP) και αποδοτικών μεθόδων επίλυσης σύνθετων προβλημάτων βελτιστοποίησης που αφορούν θέματα i) χρονοπρογραμματισμού παραγωγής, ii) ενοποιημένου χρονοπρογραμματισμού και σχεδιασμού παραγωγής και iii) σχεδιασμού και λειτουργίας δικτύων εφοδιαστικών αλυσίδων εμβολίων COVID-19.

Ο χρονοπρογραμματισμός παραγωγής αποτελεί τη διαδικασία λήψης αποφάσεων κατά την οποία κατανέμονται οι διαθέσιμοι πόροι μιας βιομηχανικής εγκατάστασης στις διάφορες διεργασίες που είναι απαραίτητες για την παραγωγή των τελικών προϊόντων. Οι πόροι αυτοί μπορεί να περιλαμβάνουν τον εξοπλισμό επεξεργασίας, αποθήκευσης και μεταφοράς υλικών, το ανθρώπινο δυναμικό και τις βοηθητικές παροχές, π.χ. ηλεκτρισμό, νερό, κ.α. Ο σχεδιασμός παραγωγής αποτελεί μια άλλη διαδικασία λήψης αποφάσεων, η οποία αφορά επίσης την κατανομή των διαθέσιμων πόρων και η οποία προηγείται του χρονοπρογραμματισμού παραγωγής, με την έννοια ότι οι αποφάσεις που λαμβάνονται κατά τον σχεδιασμό αποτελούν είσοδο του χρονοπρογραμματισμού παραγωγής. Οι διαφορές ανάμεσα σε χρονοπρογραμματισμό και σχεδιασμό παραγωγής έγκειται στον υπό μελέτη χρονικό ορίζοντα (μέρες-εβδομάδα για χρονοπρογραμματισμό και εβδομάδες-μήνες για σχεδιασμό) και στην λεπτομέρεια των αποφάσεων (πιο λεπτομερείς κατά τον χρονοπρογραμματισμό). Στην πράξη τα δύο αυτά στάδια αποφάσεων μελετώνται ξεχωριστά, ωστόσο εκτενείς έρευνες έχουν δείξει ότι η ενοποιημένη μελέτη του χρονοπρογραμματισμού και του σχεδιασμού παραγωγής οδηγεί σε σημαντική αύξηση της αποδοτικότητας μιας βιομηχανικής μονάδας.

Τα τελευταία 30 χρόνια έχει προταθεί ένα μεγάλο εύρος μεθόδων για την αντιμετώπιση αυτών των συνδυαστικών προβλημάτων, ωστόσο η πλειονότητα τους αναλώνεται σε προβλήματα που δεν αντικατοπτρίζουν την βιομηχανική πραγματικότητα. Συνήθως εμπλέκεται ένας μεγάλος αριθμός εξοπλισμού για την παραγωγή μιας πληθώρας τελικών προϊόντων, μέσω μιας ιδιαίτερα περίπλοκης παραγωγικής διαδικασίας, η οποία υπόκειται σε απαιτητικούς τεχνικούς, οικονομικούς και λειτουργικούς περιορισμούς. Έτσι, τα ρεαλιστικά προβλήματα

χρονοπρογραμματισμού παρουσιάζουν εξαιρετικά υψηλή υπολογιστική πολυπλοκότητα, με αποτέλεσμα να μην μπορούν να επιλυθούν σε χρόνους αποδεκτούς από την βιομηχανία. Επομένως, κρίνεται αναγκαία η ανάπτυξη νέων υπολογιστικών τεχνικών, οι οποίες θα συνδυάζουν αποτελεσματικότητα, απόδοση και ταχύτητα, έτσι ώστε να υποστηρίξουν τις διοικήσεις των επιχειρήσεων στη διαδικασία λήψης αποφάσεων. Προς αυτή την κατεύθυνση, στην παρούσα διατριβή πραγματοποιείται τόσο η ανάπτυξη νέων μαθηματικών μοντέλων, λαμβάνοντας υπόψη ρεαλιστικά χαρακτηριστικά, όσο και η ανάπτυξη νέων αλγορίθμων για την επίλυση των προβλημάτων σε σύντομο υπολογιστικό χρόνο.

Στο τελευταίο τμήμα του διδακτορικού, εφαρμόστηκε η τεχνογνωσία που είχε αποκτηθεί στον τομέα της μαθηματικής μοντελοποίησης, στο πρόβλημα βέλτιστης λειτουργίας και σχεδιασμού μιας εφοδιαστικής αλυσίδας για την διανομή των εμβολίων COVID-19. Το πρόβλημα αυτό αφορά κυρίως τον καθορισμό των μεταφερόμενων και αποθηκευμένων ποσοτήτων αλλά και τον προγραμματισμό των εμβολιασμών στα εμβολιαστικά κέντρα. Ο συγκεκριμένος τύπος εφοδιαστικής αλυσίδας εμφανίζει χαρακτηριστικά τα οποία δυσχεραίνουν την εύρυθμη λειτουργία του, κυρίως λόγω των ιδιαιτεροτήτων των εμβολίων τύπου mRNA, συγκεκριμένα τον περιορισμένο χρόνο ζωής των εμβολίων και τις ανάγκες αποθήκευσης σε βαθιά κατάψυξη. Συνεπώς, η «τυφλή» αποθήκευση εμβολίων δεν αποτελεί αποδοτική λύση, καθώς οδηγεί σε τεράστιο λειτουργικό κόστος, αλλά και σε απώλειες πολύτιμων δόσεων. Η βιβλιογραφία για τη βελτιστοποίηση ιατρικών εφοδιαστικών αλυσίδων περιορίζεται κυρίως σε φάρμακα και βρίσκονται ελάχιστες μελέτες για την εφοδιαστική αλυσίδα εμβολίων, οι οποίες αφορούν κυρίως την διανομή εμβολίων σε χώρες του τρίτου κόσμου. Επίσης δεν βρίσκεται μελέτη στη βιβλιογραφία για εφοδιαστικές αλυσίδες εμβολίων για την αντιμετώπιση πανδημίας, καθώς και για εμβόλια mRNA. Τα παραπάνω δημιουργούν ένα ερευνητικό κενό μεγάλου ενδιαφέροντος ιδιαιτέρως λόγω των τελευταίων εξελίξεων. Για τους παραπάνω λόγους αναπτύχθηκαν νέα μοντέλα και αλγόριθμοι επίλυσης για την βελτιστοποίηση των αποφάσεων που αφορούν την εφοδιαστική αλυσίδα εμβολίων COVID-19. Επιπλέον ορίζεται ένα νέο πρόβλημα, στο οποίο καθορίζεται ταυτόχρονα και το πρόγραμμα εμβολιασμών σε κάθε εμβολιαστικό κέντρο, μέσω της ενσωμάτωσης αποφάσεων που αφορούν τις ανάγκες σε υγειονομικό προσωπικό.

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 στις παρακάτω παραγράφους.

Αρχικά μελετάται το πρόβλημα του βέλτιστου χρονοπρογραμματισμού παραγωγής σε βιομηχανίες πολλών σταδίων, που αποτελούνται από μεικτές συνεχείς και διακριτές διεργασίες. Για την αντιμετώπιση αυτών των προβλημάτων αναπτύχθηκαν δύο νέα μαθηματικά πλαίσια. Στο πρώτο προτείνεται ένα νέο μοντέλο μεικτού-ακέραιου γραμμικού προγραμματισμού για την ελαχιστοποίηση του συνολικού χρόνου παραγωγής (makespan minimization). Συγκεκριμένα εφαρμόζεται μεικτή, συνεχής και διακριτή, χρονική αναπαράσταση, όπου η διακριτή κλίμακα χρησιμοποιείται για τους περιορισμούς ισορροπίας υλικών (material balances), ενώ η συνεχής για τις αποφάσεις χρονοπρογραμματισμού, όπως κατανομή των παρτίδων σε συσκευές, εκκίνηση και αλληλουχία διεργασιών). Επιπλέον, εισάγονται νέοι ευρετικοί περιορισμοί, οι οποίοι επιταχύνουν την επίλυση του μαθηματικού μοντέλου, χωρίς να αλλοιώνουν την ποιότητα της λύσης. Για την επίλυση προβλημάτων μεγάλης κλίμακας, αναπτύσσεται ένας νέος αλγόριθμος διάσπασης, όπου σε κάθε επανάληψη βελτιστοποιείται το πρόγραμμα παραγωγής για ένα υποσύνολο των παραγγελιών. Με το πέρας κάθε επανάληψης σταθεροποιούνται οι δυαδικές μεταβλητές για το υποσύνολο που εξετάζεται. Με την τελευταία επανάληψη προκύπτει το τελικό πρόγραμμα παραγωγής. Στο δεύτερο μαθηματικό πλαίσιο προτείνεται μια πρωτοποριακή μέθοδος για τη μείωση της πολυπλοκότητας του συνδυαστικού προβλήματος βελτιστοποίησης. Με βάση αυτή τη νέα μέθοδο, αναπτύχθηκαν δύο νέα μοντέλα μεικτού-ακέραιου γραμμικού προγραμματισμού, ένα γενικής προτεραιότητας (general precedence) για την ελαχιστοποίηση του χρόνου παραγωγής και ένα γενικής προτεραιότητας ως προς κάθε συσκευή (unit-specific general precedence) για την ελαχιστοποίηση του χρόνου εναλλαγών (changeover minimization). Τέλος, το μοντέλο εντάσσεται σε ένα αλγόριθμο διάσπασης, παρόμοιο με αυτό που εφαρμόστηκε στο πρώτο μαθηματικό πλαίσιο, ώστε να υπάρχει δυνατότητα επίλυσης προβλημάτων βιομηχανικής κλίμακας. Η κύρια διαφορά των δύο μεθόδων έγκειται στην λεπτομέρεια των αποφάσεων που λαμβάνονται, καθώς η πρώτη εξάγει λεπτομερή προγράμματα για όλα τα στάδια

παραγωγής, ενώ η δεύτερη μόνο για τα συνεχή. Ωστόσο, η δεύτερη μέθοδος είναι υπολογιστικά σαφώς ανώτερη της πρώτης.

Τα παραπάνω μοντέλα εφαρμόζονται σε ένα πραγματικό βιομηχανικό πρόβλημα μεγάλης κλίμακας. Συγκεκριμένα, μελετήθηκε η παραγωγική διαδικασία της ισπανικής βιομηχανίας τροφίμων «Frinsa del Noroeste». Αυτή αποτελείται από πολλά στάδια παραγωγής, συνεχούς και διαλείπουσας, λειτουργίας, σε κάθε ένα από τα οποία λειτουργούν παράλληλα πολλαπλές μηχανές, ενώ σε εβδομαδιαία βάση εξυπηρετούνται πάνω από 100 παραγγελίες. Πραγματοποιήθηκαν εκτενής μελέτες σε προβλήματα βέλτιστου χρονοπρογραμματισμού που αντιστοιχούν στις εβδομάδες που πιέζουν περισσότερο την παραγωγική διαδικασία. Χρησιμοποιήθηκαν πραγματικά δεδομένα ζήτησης και λειτουργίας της μονάδας, τα οποία εξήχθησαν από τα υπολογιστικά συστήματα της εταιρείας, για ορισμένες ιστορικές εβδομάδες. Χρησιμοποιώντας το πρώτο μαθηματικό πλαίσιο, προτείνονται σχεδόν βέλτιστα προγράμματα παραγωγής σε μία ώρα, τα οποία μειώνουν το χρόνο παραγωγής κατά ~15%, συγκριτικά με τα προγράμματα παραγωγής που είχαν προτείνει οι μηχανικοί παραγωγής. Στον αντίποδα η εφαρμογή του δεύτερου μαθηματικού πλαισίου απαιτεί λιγότερο υπολογιστικό χρόνο (~15 λεπτά) για την εξαγωγή λύσεων πλησίον των βέλτιστων. Η ταχύτητα επίλυσης επιτρέπει τον ταχύτατο επαναπρογραμματισμό σε περίπτωση απρόοπτων αλλαγών (π.χ. αλλαγή παραγγελιών), αλλά και την αξιολόγηση εναλλακτικών σεναρίων από τους μηχανικούς παραγωγής. Επίσης με το δεύτερο μαθηματικό πλαίσιο δίνεται η δυνατότητα μελέτης προβλημάτων ελαχιστοποίησης του χρόνου εναλλαγών. Με τη συγκριτική μελέτη μεταξύ των προγραμμάτων παραγωγής που εξάγονται από τα ανεπτυγμένα μοντέλα του δεύτερου μαθηματικού πλαισίου και αυτών που προτείνονται από τους μηχανικούς παραγωγής της βιομηχανίας, διαπιστώνεται σημαντική αύξηση της αποδοτικότητας της μονάδας, μέσω της μείωσης του χρόνου παραγωγής (~10%) ή της μείωσης του χρόνου εναλλαγών (~15%).

Επιπλέον μελετήθηκε ο χρονοπρογραμματισμός και σχεδιασμός παραγωγής σε βιομηχανίες ζύθου. Συγκεκριμένα προτείνεται ένα νέο μοντέλο μεικτού-ακέραιου γραμμικού προγραμματισμού για τον ενοποιημένο βέλτιστο χρονοπρογραμματισμό και σχεδιασμό παραγωγής, ώστε να ελαχιστοποιηθεί το κόστος παραγωγής σε μια ζυθοποιία. Η δυσκολία στην εξαγωγή βέλτιστων αποφάσεων χρονοπρογραμματισμού σε μια ζυθοποιία έγκειται κυρίως στον πολύ μεγάλο χρόνο παράδοσης, ο οποίος δημιουργεί την ανάγκη μελέτης εκτεταμένου χρονικού ορίζοντα, συνεπώς τη δημιουργία μεγάλων

μοντέλων MILP. Το πρόβλημα αυτό αντιμετωπίζεται με την εφαρμογή μεικτής χρονικής αναπαράστασης και την διάσπαση του χρονικού ορίζοντα σε δύο τμήματα. Στο πρώτο λαμβάνονται αποφάσεις σχεδιασμού και χρονοπρογραμματισμού παραγωγής, ενώ στο δεύτερο μόνο σχεδιασμού παραγωγής. Παρουσιάζεται μια εκτενής συγκριτική μελέτη μεταξύ του προτεινόμενου μοντέλου και του μοναδικού ανάλογου μοντέλου της βιβλιογραφίας, σε ένα μεγάλο εύρος προβλημάτων, η οποία αποδεικνύει την ανωτερότητα του αναπτυγμένου μοντέλου. Επιπλέον, αναπτύχθηκε μια στρατηγική επίλυσης προβλημάτων μεγάλης πολυπλοκότητας, η οποία αποτελείται από δύο στάδια. Στο πρώτο κατασκευάζεται μια αρχική λύση, η οποία στη συνέχεια βελτιώνεται μέσω μιας επαναληπτικής εξοντωτικής διαδικασίας εφαρμογής τελεστών χαλάρωσης και βελτιστοποίησης των μεταβλητών του προβλήματος (fix-and-optimize). Η παραπάνω στρατηγική επίλυσης εφαρμόζεται επιτυχώς σε ένα ρεαλιστικό βιομηχανικό πρόβλημα.

Στο τελευταίο τμήμα της διδακτορικής διατριβής μελετάται το πρόβλημα βελτιστοποίησης του σχεδιασμού και της λειτουργίας εφοδιαστικών αλυσίδων εμβολίων COVID-19. Συγκεκριμένα μελετάται η ταυτόχρονη βελτιστοποίηση των αποφάσεων της εφοδιαστικής αλυσίδας, π.χ. μέγεθος στόλου, επίπεδα αποθηκών, αλλά και των αποφάσεων σχετικά με το πρόγραμμα εμβολιασμών στα εμβολιαστικά κέντρα. Αυτό το πρόβλημα προγραμματισμού εξετάζεται για πρώτη φορά, οπότε η μελέτη αυτή το εισάγει στη διεθνή βιβλιογραφία. Για την αντιμετώπιση αυτού του συνδυαστικού προβλήματος αναπτύσσεται ένα νέο μαθηματικό μοντέλο για την ελαχιστοποίηση του κόστους διανομής εμβολίων COVID-19. Η εφοδιαστική αλυσίδα αποτελείται από τρία επίπεδα, τα εργοστάσια παραγωγής, τις κεντρικές αποθήκες εμβολίων και τα εμβολιαστικά κέντρα. Εξετάζεται χρονικός ορίζοντας δύο εβδομάδων, ώστε να υπερκαλύπτεται η μειωμένη διάρκεια ζωής ορισμένων εμβολίων σε συνθήκες απλής ψύξης (πέντε μέρες). Λαμβάνονται υπόψη όλες οι τεχνικές ιδιαιτερότητες του προβλήματος, όπως η μειωμένη διάρκεια ζωής εμβολίων και ο χρόνος που απαιτείται για τη μεταφορά των εμβολίων. Η επίλυση του μαθηματικού μοντέλου οδηγεί σε βέλτιστες αποφάσεις όσον αφορά τα επίπεδα αποθηκευμένων εμβολίων στις κεντρικές αποθήκες και τα εμβολιαστικά κέντρα, τις μεταφερόμενες ποσότητες ανάμεσα στα επίπεδα της εφοδιαστικής αλυσίδας, το ημερήσιο πρόγραμμα εμβολιασμών, το νοσηλευτικό προσωπικό και το μέγεθος του στόλου οχημάτων. Η αποτελεσματικότητα του μοντέλου δεν επαρκεί για την ταχεία επίλυση προβλημάτων που αντιστοιχούν σε εθνικά εμβολιαστικά προγράμματα, οπότε προτείνεται ένας αλγόριθμος επίλυσης για

προβλήματα μεγάλης πολυπλοκότητας. Αρχικά τα εμβολιαστικά κέντρα κατανέμονται στις κεντρικές αποθήκες βάση γεωγραφικών κριτηρίων. Στη συνέχεια τα εμβολιαστικά κέντρα συγκεντρώνονται σε συστάδες (clusters) με βάση τις περιφερειακές ενότητες στις οποίες ανήκουν. Έπειτα λύνεται ένα συγκεντρωτικό μοντέλο (με βάση τις παραμέτρους για τις συστάδες) και τέλος η λύση αυτή χρησιμοποιείται στο επόμενο στάδιο, οπού λύνεται ένα λεπτομερές μοντέλο για όλα τα εμβολιαστικά κέντρα. Η παραπάνω μέθοδος εφαρμόστηκε επιτυχώς σε ένα πρόβλημα που προσομοιώνει το εμβολιαστικό πρόγραμμα της Ελλάδας. Σε αυτό εξετάζονται πέντε κεντρικές αποθήκες, 351 εμβολιαστικά κέντρα, πολλαπλές γραμμές εμβολιασμού ανά κέντρο και τέσσερα διαφορετικά εμβόλια. Ως αποτέλεσμα επιτυγχάνονται σχεδόν βέλτιστες λύσεις σε σύντομο χρονικό διάστημα, ενώ τα εμβόλια που πετιούνται λόγω κακής διαχείρισης της εφοδιαστικής αλυσίδας είναι ελάχιστα. Τέλος, μελετάται ο επανασχεδιασμός της εφοδιαστικής αλυσίδας, με χρήση ενός αλγόριθμου κυλιόμενου ορίζοντα, σε περίπτωση μεταβολής της ζήτησης, λόγω ακύρωσης ραντεβού ή μη-έλευσης πολιτών σε προκαθορισμένα ραντεβού.

Acknowledgements

In November of 2016 I was finishing my master studies in Germany and looking for the next chapter of my career. As an electrical engineer I never expected this to be a PhD in the Chemical Engineering Department of the Aristotle University of Thessaloniki. However, I took this leap of faith and four and a half years later, I can tell, that faith and hard work did not disappoint me. But I could have never done this alone. These few paragraphs are devoted to the people who walked with me, in flesh and in spirit, and helped me complete the leap, safely, back to the ground.

First and foremost, I would like to thank my supervisor Professor Michael C. Georgiadis for his unending support throughout all these years. He invited me into a beautiful journey and introduced me to the field of mathematical optimization. His guidance and constant feedback have been invaluable. Furthermore, I wish to express my gratitude to Dr. Georgios Kopanos and Dr. Chrysa Ziogou who significantly assisted me in the beginning of my research. Moreover, I wish to thank Project CoPro of the European Union's Horizon 2020 research and innovation program for financially supporting this research. The successful completion of the real-life industrial applications would not be possible without the help of ASM Soft and Frinsa del Noroeste. Specially, I heartily thank Daniel Adrian Cabo for his high-quality work and the fruitful collaboration we had. I would also like to thank the members of my academic committee Professor Dimitrios Vlachos and Dr. Spyridon Voutetakis for the assistance and feedback they provided.

Throughout the course of my PhD research, I was blessed to meet and work with wonderful people. First, I would like to thank the friends I made in the 10 months I worked in the Centre of Research and Technology Hellas. Panagiotis K., Thodoris Z., Alexis K. and Michael B., I am lucky to call you my friends. Our laugh-filled conversations made many difficult days bearable. Then, I would like to thank my colleagues in the Process Systems Engineering laboratory of the Chemical Engineering Department. There isn't a single line on this thesis that I have not discussed with my friend Apostolis E. Our conversations, his feedback and suggestions were crucial in the constant improvement of this work's quality. Also, I wish to thank Dr. Panagiotis Karakostas, Romuald G., Christos D.and Achilleas A., who created a pleasant working environment and with whom we shared many thoughts and emotions.

Last but not least, I would like to express my gratitude to my parents Panagiotis and Katerina, and my brother Thanasis for being an unlimited source of unconditional love and support throughout my life. My warmest thanks go to my partner Elena for her understanding, constant encouragement, and belief. She overflows my life with love and happiness, transforming these difficult years into a beautiful experience.

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Abbreviations

MILP	Mixed Integer Linear Programming
CPU	Central Processing Unit
STN	State Task Network
RTN	Resource Task Network
TSP	Travelling Salesman Problem
PSE	Process Systems Engineering
ERP	Enterprise Resource Planning
FMCG	Fast Moving Consumer Goods
SCN	Supply Chain Network
SCM	Supply Chain Management
SCO	Supply Chain Optimization
VSC	Vaccine Supply Chain
WHO	World Health Organisation
WHO-EPI	World Health Organization's Expanded Program on Immunization
COVID-19	Coronavirus disease of 2019
MES	Manufacturing Execution System
OEE	Overall Equipment Effectiveness
DCA	Discrete and Continuous Algorithm
GEG	Georgiadis-Elekidis-Georgiadis model presented in Chapter 4
GEG_S1	Georgiadis-Elekidis-Georgiadis model for the first stage of the constructive step presented in Chapter 4
GEG_S2	Georgiadis-Elekidis-Georgiadis model for the second stage of the constructive step presented in Chapter 4
FO_F	Fix-and-Optimize Forward
FO_B	Fix-and-Optimize Backward
FO_F21	Fix-and-Optimize Forward first Stage 2 then Stage 1
FO_B21	Fix-and-Optimize Backward first Stage 2 then Stage 1
BSAM	Baldo Santos Almada Morabito model

IMP.A Improvement approach A used in Chapter 4

IMP.B Improvement approach B used in Chapter 4

Chapter 1

Introduction

1.1 Motivation and objectives

Process industries operate in an environment characterized by increasing competitiveness and minuscule profit margins. Therefore, they must strive more than ever for efficiency and increased productivity. In addition to significant economic benefits, the better coordination of production leads to important reduction in energy needs, thus allowing industries to achieve a more environmentally friendly production process. The decision-making process that allows for the efficient management of production and thus can directly affect the productivity of any facility is production scheduling. This process refers to the efficient allocation of resources, such as equipment, utilities and manpower, over a given time horizon of interest, e.g. daily, weekly etc., so that all required tasks are executed and incoming orders are satisfied (Pinedo 2016). The importance of optimal production scheduling has been long recognised by academia; therefore, a plethora of works written across different scientific communities can be found in literature (Harjunkoski et al. 2014). An abundance of optimization-based algorithms has been proposed to address the production scheduling problem. Most of them express the production scheduling problem as a mixed-integer linear programming (MILP) problem, since it proved to be extremely flexible and rigorous, while ensuring optimality. However, production facilities comprising of multiple batch and continuous operations have received nearly no attention compared to other type of production processes, despite being the norm in a large variety of industries, such as, food and beverage, chemicals, pharmaceuticals, etc. Therefore, efficient mathematical frameworks for the optimal production scheduling of mixed batch and continuous processes is a known research gap. Concerning the above observation, we study the optimal production

scheduling of facilities comprising of mixed batch and continuous processes by developing novel mathematical frameworks.

Digitalization of manufacturing is attracting a lot of attention within all process industries and is expected to have a significant impact on how the industry operates (Isaksson, Harjunkoski, and Sand 2017). However, in terms of production scheduling, the current industrial reality is different. In most cases schedules are manually generated by production engineers or operators, based on rules and heuristics, that arise from their multiyear experience and understanding of the production process. Due to the complex nature of real scheduling problems, that involve a large number of items, like tasks, intermediate and final products, multiple parallel machines, many processing stages and production routes, manually generating good schedules becomes an extremely difficult and tedious task. Hence, numerous iterations and a significant number of working hours are required daily, which generally lead to sub-optimal results. In some cases, industries utilize commercially available scheduling tools (Intelligen Inc.), in order to automate the procedure and to generate fast and feasible production schedules. However, the schedules are created based on simple heuristics that mostly ensure their feasibility. Consequently, either when schedules are manually generated by the engineers or when simulation-based tools are employed, the extracted solutions are far from being optimal. Furthermore, generated and later executed schedules cannot be evaluated in terms of their efficiency, so the managers cannot assess the true potential benefits realized on the plant. As a result, productivity is reduced, resources are underutilized, customers are dissatisfied and there are significant profit losses, which result to a decrease in the industries' competitiveness. The deployment of optimization-based tools in industrial problems can address these issues by assisting the production engineers into systematically improving their decisions, thus leading to important economic, environmental and social benefits (Harjunkoski 2016). Therefore, a high interest has been expressed for real-life industrial case studies and problem specific solutions have been generated for real industrial facilities. Moreover, the ever-increasing computational power, allowed the handling of larger problem instances. However, there is still a significant gap between the academic research and the industrial practice, as only a few contributions have been successfully applied in real-life scheduling problems. Due to the lack of real-life applications, all proposed mathematical frameworks are employed on large-scale instances of industrial problems.

The unprecedented effects of the SARS-COV-2 virus, which resulted in the COVID-19 pandemic, have risen an immense global interest regarding the development and distribution of safe and effective vaccines. Until the completion of this thesis, more than 160 million people have been already infected and close to 3.5 million could not overcome this catastrophic disease worldwide. In addition, the necessitated protective measures and lengthy lockdowns have a severe financial impact on society. The urge to rapidly decrease the toll of COVID-19 on health and global economy led to significant scientific breakthroughs and the authorization of various vaccine candidates within a record time. While the focus in the vaccine world has been on developing the required vaccines and measuring their effectiveness, struggle to understand and properly address the issues of the Vaccine Supply Chain (VSC), greatly reduces the impact of any vaccination program (Lee and Haidari 2017). Mass vaccination of the world's population will achieve herd immunity, the first step for the progressive transition to the pre-COVID-19 normalcy. As a result, the biggest vaccination program in human history is currently in action pushing the COVID-19 VSC to its limits. Furthermore, special characteristics of the COVID-19 VSC, like limited shelf life and storage requirements in freezing conditions, makes its management a logistical challenge. Multiple decisions are required e.g., on central hub locations, vaccination locations, facility layouts, the order people are vaccinated, staffing levels etc. Efficient and effective planning and operation of the supply chain is critical for the success of the vaccination program, otherwise, numerous valuable doses will be wasted, and the program's progress will slow down, imposing important financial losses. Due to the aforementioned difficulties, the COVID-19 VSC optimization problem, has been addressed only by a handful of contributions, which mainly focus on manufacturing issues of mRNA vaccines (Kontoravdi, Shattock, and Shah 2021), while the optimal distribution of the COVID-19 vaccines has never been addressed. As a result, the current scientific knowledge is expected to be greatly broadened with the introduction of an optimization-based framework for the optimal planning of the COVID-19 VSC.

The primary objectives of this thesis are:

- To develop novel optimization-based frameworks based on MILP techniques for the optimal production scheduling of multiproduct mixed batch and continuous facilities.

- To develop a new MILP model that tackles the integrated optimal production planning and scheduling problem in mixed batch and continuous processes.
- To propose efficient solution strategies, which combine decomposition techniques, heuristic algorithms, and MILP models, in order to generate optimal or near-optimal solutions for large-scale problem instances in low Central Processing Unit (CPU) times.
- To introduce a new problem in the open literature that simultaneously considers short-term planning decisions for the COVID-19 VSC along with the vaccination plans in the associated vaccination centres.
- To develop appropriate MILP-based solution strategies capable of solving a nation-wide COVID-19 VSC planning problem.
- 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 data, or simulated data that correspond to real-life conditions.

1.2 Production scheduling

1.2.1 Classification of scheduling problems

Traditionally, scheduling problems are defined in terms of a triplet α/β/γ (Pinedo 2016). The α field describes the production environment, while the β field denotes the special characteristics and production constraints. Finally, field γ describes the problem's objective e.g., minimization of cost. The entries of this triplet can be extremely diverse between process industries, since a great variety of aspects needs to be considered when developing optimization models for process scheduling. As a result, many classes of scheduling problems exist. However, the general production scheduling problem can be summarized in the following.

Given are:

- Facility data, e.g., processing stages and units, storage vessels, processing rates, unit to task compatibility.

- Production targets that need to be satisfied.
- Availability of raw materials and resource limitations, e.g., maintenance of units, availability of utilities.

The first term denotes the characteristics of the facility and can be considered static input to the scheduling problem, since it remains the same for all problem instances of a facility, unless any redesign studies are considered. The remaining terms are inputs from other decision-making processes in the manufacturing environment. Scheduling is not a standalone problem; it is part of the manufacturing supply chain and has strong connections to other planning functions. Production targets and materials availability come from the planning level, while resource availability is an output of the control level, thus there is a significant flow of information from other planning functions to scheduling (Figure 1.*1*).

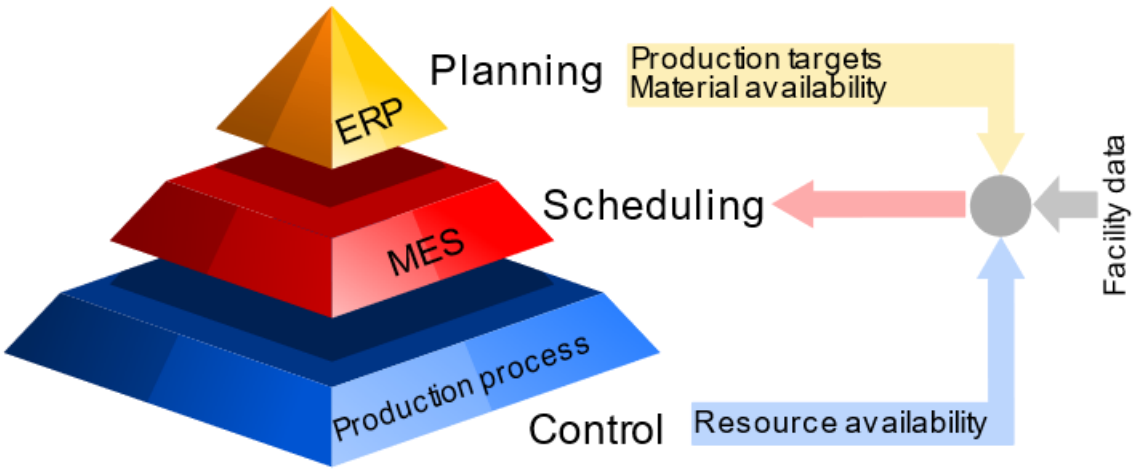

Figure 1.1: Information flow towards scheduling level

Main goal is to propose a schedule that reaches the production targets, while respecting all operational, logistical, and technical constraints, and achieve a certain objective, such as the maximization of profit, the minimization of the total cost, earliness and/or tardiness, and production makespan.

The general scheduling problem seeks to optimally answer the following questions (Figure 1.2):

- What tasks must be executed to satisfy the given demand (batching/lot-sizing)?
- How should the given resources be utilized (task-resource assignment)?
- In what order are batches/lots processed (sequencing and/or timing)?

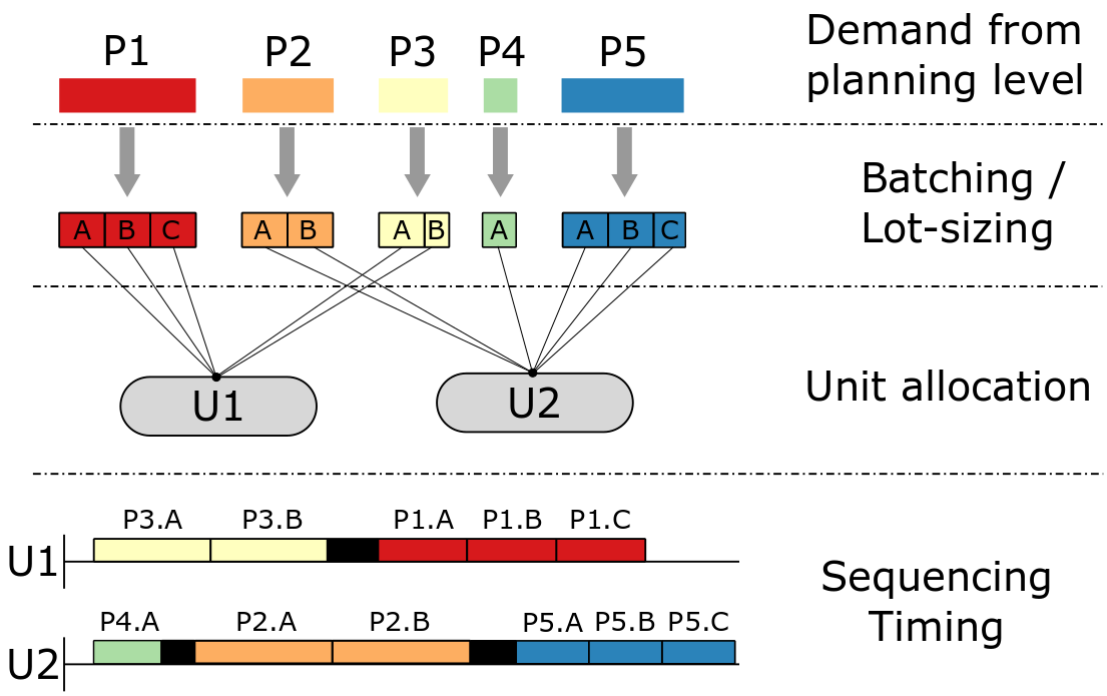

Figure 1.2: Decisions of production scheduling in the process industries

Note that depending on the specifics of the problem at hand, some of these decisions are not considered in the scheduling level. When developing a model for the optimal scheduling problem all characteristics of the production must be considered to ensure the feasibility of the proposed schedules. However, the production needs to be portrayed in an abstract way to reduce the computational complexity of the problem. This is even more crucial when dealing with real-life industrial applications, which are typically characterized by complex structures, ever-expanding product portfolios and a huge number of constraints that must be considered.

Scheduling is a critical decision-making process in all process industries, from the chemical and pharmaceutical to the food and beverage and the petrochemical sector. Besides the aforementioned general description of scheduling, industrial applications display strong differences to each other, due to the facility itself, the production policy or market and business considerations. First step when approaching an industrial

scheduling problem is to identify its problem specifics, in order to accurately portray the problem at hand. Moreover, a strong correlation between different classes of scheduling problems and the available mathematical modelling frameworks exists. The scheduling problems found in process industries are classified in terms of: (a) the production facility, (b) the interaction with the rest of the production supply chain, and (c) the specific processing characteristics and constraints. A short description of these terms follows, and further details can be found in the excellent reviews of Maravelias (2012) and Harjunkoski et al. (2014).

1.2.1.1 The production facility

At this point we should note that the following analysis focuses on production scheduling. However, many scheduling problems in the process industries target to the optimization of material transfer operations rather than production operations. Characteristic examples are crude oil and pipeline scheduling. With this in mind, the production facility is classified based on the type of process (batch/continuous) and the production environment (sequential or network).

1.2.1.1.1 Process type

The type of production processes found in the process industries can be defined as continuous or batch. In continuous mode, units are continuously fed and yield constant flow. Continuous processes are appropriate for mass production of similar products, since they can achieve consistency of product quality, while manufacturing costs are reduced, due to economies of scale. The main characteristic of batch processes is that all components are completed at a unit before they continue to the next one. Batch production is advantageous for production of low-volume high-added value products, or for production of seasonal demands which are difficult to forecast. One of the main advantages of batch production is the reduced initial capital investment, therefore it is especially profitable for small business or trial runs of new facilities. From a scheduling point-of-view, both batch and continuous processes require the same type of decisions. Tasks are characterized as batches in batch and lots in continuous processing. Assignment (batches/lots to units), sequencing (between batches/lots) and timing (of batches/lots) decisions are identical, while selection and sizing of tasks (batching/lot-sizing) display more degrees of freedom in continuous processes. Capacity restrictions in

continuous processes refer to processing rates and processing times and are usually unrestricted, thus a given order can be satisfied in a single lot (campaign) or multiple shorter ones. On the other hand, batch production is capacitated by the amount of processed material that a unit can process, thus affecting the number and size of batches to be scheduled. Another difference lies in the way inventory levels are affected. At this point, it is worth mentioning that many facilities are characterized by more than one type of processes. A characteristic example is the "make-and-pack" type of production, where several batch or continuous processing stages are followed by a packing (continuous) stage. This production flow is very common in the food and beverage and the consumer goods industries and requires the consideration of both the characteristics of batch and continuous production processes (Baumann and Trautmann 2012; Georgiadis et al. 2020).

1.2.1.1.2 Production environment

Production facilities can be classified as sequential, or network based on the material handling restrictions. In sequential processing, each batch/lot follows a sequence of stages based on a specific recipe. Throughout its recipe a batch retains its identity, since it cannot be mixed with other batches or split into multiple downstream batches. Network facilities are characterized as more general and complex and have usually an arbitrary topology. Moreover, no restrictions exist for the handling of input and output materials, thus mixing and splitting operations are included. Based on their topological characteristics, sequential facilities can be further categorized into the following:

- Single stage: Production facility that consists of just one processing stage, which may consist of a single unit or multiple parallel units. The product to unit compatibility may be fixed (batch can be processed in a single unit) or flexible (batch can be processed in multiple units), but in all cases each batch must be processed in a single unit.
- Multistage: Each batch must be processed in more than one processing stages, each consisting of a single unit or multiple parallel units. The multistage environment can be further categorized into multiproduct and multipurpose, depending on the imposed routing restrictions. Multiproduct facilities are equivalent to flowshop environments in discrete manufacturing, where all products go through

the same sequence of processing stages. In contrast, a facility is characterized as multipurpose when the routings are product-specific, or when a processing unit belongs to different processing stages depending on the product, thus being equivalent to jobshop environments in discrete manufacturing.

Early studies mainly focused on scheduling problems that are characterized as sequential (Egli and Rippin 1986; Vaselenak, Grossmann, and Westerberg 1987). Process industries with a sequential environment are very similar to discrete manufacturing, from a scheduling point-of-view. Sequential facilities can be easily modelled in terms of batches and production stages, like jobs and operations in discrete manufacturing. However, this does not hold true for network facilities, thus they cannot be modelled in a similar straightforward manner. In the early 90s, the research team of Prof. Sargent in Imperial College London was the first to propose general representations for network facilities. In particular, they introduced the concepts of the State-Task-Network (STN) (Kondili, Pantelides, and Sargent 1993; Shah, Pantelides, and Sargent 1993) and the Resource-Task-Network (RTN) (Pantelides 1994), which allowed the development of optimization models for scheduling problems of such complex structures. A classification of the production environments for process industries is illustrated in Figure 1.3.

1.2.1.2 Interaction with other planning functions

Scheduling is strongly interconnected to the rest of the planning functions of the manufacturing supply chain; therefore, it cannot be approached as a standalone problem. The interactions between scheduling and the other decision-making processes in a manufacturing environment must be accounted for, since they determine significant aspects of the scheduling problem; in particular: a) the input parameters of the scheduling problem, b) the decisions to be optimized by the scheduler, c) the type of scheduling problem to be solved and d) the problem's objective.

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, 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-fixed, and the scheduling decisions are narrowed

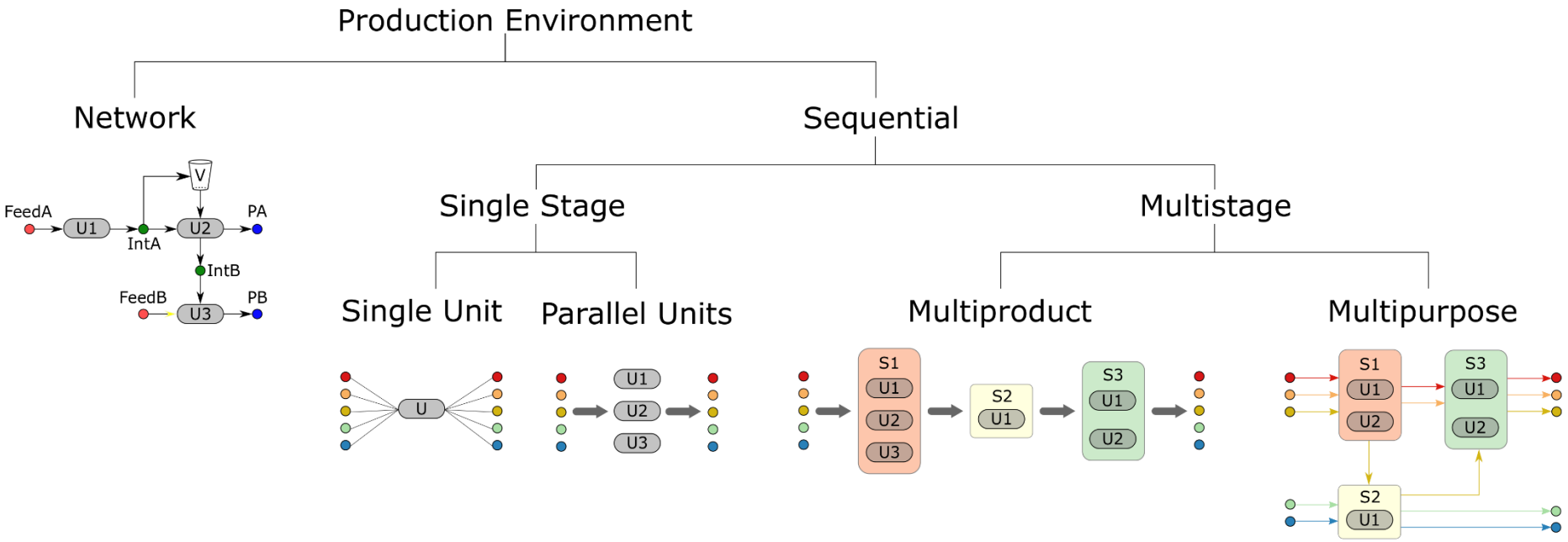

Figure 1.3: Categorization of scheduling problems based on the production environment

down to just unit to task assignment, sequencing, and timing of tasks. There is also an important flow of information between scheduling and control; more specifically the optimized schedule provides the reference points to the control level while resource availability is in turn provided to the scheduling level. Most studies until the early 2000s, approach production scheduling as a standalone problem. However, the scientific community acknowledged the importance of integrating the decision-making process of the various functions (planning, scheduling and control) that comprise the manufacturing supply chain of a process industry (Grossmann 2005). The integrated planning and scheduling problem has been studied in multiple works over the last decades (Li and Ierapetritou 2010; Kopanos, Puigjaner, and Maravelias 2011) and also implemented in industrial case studies with great success (Baldo et al. 2014; Sel et al. 2015; Georgiadis, Elekidis, and Georgiadis 2021). In contrast the integrated scheduling and control and integrated planning, scheduling and control problems have been only recently examined (Du et al. 2015; Charitopoulos, Dua, and Papageorgiou 2017).

The demand volume and variability defined by the market environment in which an enterprise operates plays a pivotal role, since it specifies the type of the scheduling problem to be solved. On the one hand, high-volume production with relative constant demand based on forecasting favors a "make-to-stock" production policy, while the low-volume production with irregular demand follows a "make-to-order" policy. In the former the generated schedule is repeated periodically ("cyclic scheduling"), while in the latter a short-term schedule must be frequently generated. Finally, the objective of the production scheduling problem is usually imposed by the relation between the capacity of the plant and the demand to be satisfied. More specifically, when the demand overcomes the capacity of the plant, then objectives such as, the minimization of backlogs or the maximization of throughput are chosen. On the contrary, if the capacity is enough to satisfy the demand, the production goal is the minimization of total cost.

1.2.1.3 Processing characteristics and constraints

Scheduling problems may refer to facilities that exhibit various special processing characteristics and constraints. These aspects complicate the problem but must be considered, in order to ensure the feasibility of the generated production schedules. In

the next section we will shortly review some of them. Further details can be found in (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) inducing an additional cost 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 classification illustrates the complexity of scheduling problems and the tremendous diversity of aspects that must be accounted for when dealing with real industrial applications (Figure 1.4). The inherent diversification of scheduling problems in the process industries hindered the initial efforts of the academic community to propose a unified general mathematical framework. Therefore, research turned into the development of less general methods which 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.

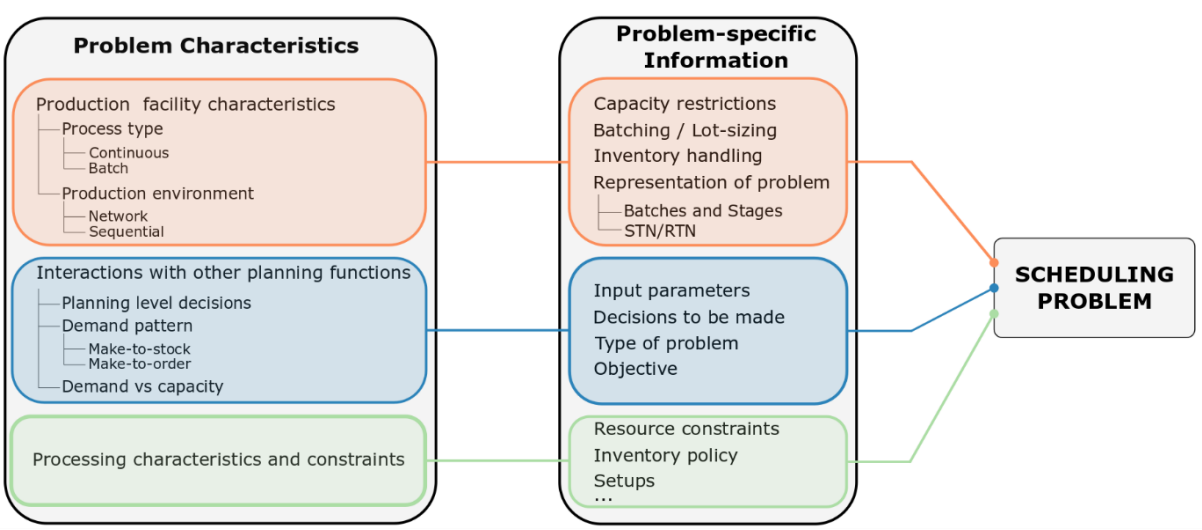

Figure 1.4: Information extracted from problem characteristics

1.2.2 Classification of modelling approaches

As mentioned in the previous subsection, scheduling problems in the process industries are defined by extremely diverse features (e.g., production environment, processing characteristics etc.), while different aspects need to be taken into account based on external parameters, like the market environment in which the industry under study operates. Therefore, the initial attempts of proposing a mathematical framework that would constitute a panacea to all scheduling problems, were unsuccessful and soon solutions that take advantage of the problem-specific characteristics emerged. The struggle to overcome the computational complexity associated with scheduling problems, gave rise to numerous scheduling models. It should be noted that in this thesis we focus on optimization-based approaches, more specifically, the models presented are mixed-integer programming (MIP) models. Nevertheless, we should mention that an abundance of alternative solution approaches, e.g. constraint programming models (Zeballos, Novas, and Henning 2011; Malapert, Guéret, and Rousseau 2012), heuristics (Bassett, Pekny, and Reklaitis 1996) and metaheuristics (Panek et al. 2008), exist in the literature. These methods can provide fast and feasible solutions, thus being a very attractive solution for industrial case studies. However, their superiority in terms of computational time comes with a cost since optimality of the generated schedules is not ensured. To combine the advantages of both optimization and non-optimization approaches, hybrid methods have emerged that are able to provide near-optimal solutions in low computational time (Kopanos, Méndez, and Puigjaner 2010).

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.

1.2.2.1 Optimization decisions

The optimization decisions are affected by the handling of batches/lots. As we underlined in subsection 1.2.1.2, batching decisions may be optimized in the planning level, thus be prefixed and be an input to the scheduling problem. Even if this is not the case, the scheduler has the flexibility to decide whether the batching decisions will be part of the optimization model. For example, the decision-maker can heuristically specify the number and size of batches and then utilize an optimization approach for the unit allocation, sequencing, and timing decisions. Usually models for sequential environments favor this two-step approach. In contrast, a monolithic approach, consisting of batching/lot-sizing, unit assignment, sequencing, and timing decisions, is used for network environments. Few recent works have proposed a monolithic approach to deal with scheduling problems in sequential environments (Prasad and Maravelias 2008; Sundaramoorthy and Maravelias 2008; Lee and Maravelias 2017b). In some special cases, like in the single machine problems, only sequencing and timing decisions are optimized, thus reducing the scheduling problem to a traditional Travelling Salesman Problem (TSP).

1.2.2.2 Modelling elements

According to the entity used to enforce the resource constraints on processing units, modelling approaches are classified into i) batch-based and ii) material-based. In sequential environments, where the identity of each batch remains the same throughout the processing stages, batch-based approaches are used. On the contrary a material-based approach is favoured, when dealing with network environments, where batches are mixed or split. It is important to mention that the modelling elements used are tied to the optimization decisions. More specifically, 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.

The modelling elements are strongly tied with the representation of the manufacturing process, which is the core of every scheduling model. Goal of a successful representation is to translate the real problem (orders, units, stages) into mathematical entities (variables, constraints) in an abstract way, that will allow for the fast generation of optimal and feasible schedules. Even a simple manufacturing process may consist of multiple operations, therefore the use of a simplified representation is essential. The oldest type of manufacturing process representation is used to model scheduling problems of sequential production environment and is based on (i) processing stages, (ii) processing units in each stage and (iii) 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 et al. (1993) and Pantelides (1994), who introduced the STN and RTN, both based on the modelling of materials, tasks, units and utilities. The STN represents manufacturing processes as a collection of material states (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 originally introduced for scheduling problems in network environments, recent works have addressed problems in sequential environments using the RTN representation (Castro, Grossmann, and Novais 2006; Velez and Maravelias 2013).

1.2.2.3 Time representations

The most studied topic and the one that mostly differentiates optimization models for scheduling is the representation of time. Depending on the way sequencing and timing of tasks are considered, modelling approaches are categorized in two broad approaches, in particular precedence-based and time-grid-based. Based on their type, precedence-based models are classified into general, immediate, and unit-specific general precedence models and time-grid-based into discrete and continuous. Continuous-time formulation may employ single or multiple-time grids. Figure 1.5 illustrates the various time representation approaches in optimization models for scheduling.

All precedence-based models consist of unit-task allocation and task-task sequencing constraints (Pinto and Grossmann 1998). The latter are expressed as precedence relationships between tasks processed in the same unit, while the former

ensure that each batch/lot is processed by exactly one unit in each stage. Binary sequencing variables are introduced to enforce the precedence relationships and ensure the generation of a feasible schedule (no processing of multiple tasks simultaneously in the same unit). Another main characteristic of any precedence model is that the timing variables are not mapped onto an external time reference, rather their exact values are specified within the scheduling horizon based on the interactions (timing constraints) between pairs of batches/lots or between processing stages of the same batch. Two types of precedence variables exist: (i) general, where precedence relationships are established between all pairs of batches/lots and (ii) immediate, where they are established only between consecutive pairs. General precedence models require fewer variables, so they are more computationally efficient. However, these models do not identify subsequent tasks, making it difficult to consider changeover costs and heuristics, such as pre-fixing or forbidding certain processing sequences. To overcome this limitation Kopanos et al. (2010) proposed the unit-specific general precedence approach that combines both general and immediate sequencing variables. In all cases precedence-based models can provide high quality solutions with low computational cost, thus being an attractive alternative when dealing with real-life industrial problems. One of the main disadvantages of this approach is the quadratic increase of the size of the model with the number of batches/products considered. The use of information such as product families or pre-fixing of sequences mitigates this phenomenon and vastly improves the efficiency of the models (Kopanos, Puigjaner, and Georgiadis 2010).

Time-grid-based models enforce timing and sequencing constraints through the utilization of a single or multiple time grids, onto which events (e.g., starting or completion of task) are mapped. A great variety of time-grid-based approaches exist depending on the representation of events (time slots, global periods, time points or events), which are classified into discrete and continuous. In discrete-time models the time-grid is portioned into a pre-fixed number of global time periods of a known duration, both of which need to be specified by the modeler. Most discrete formulations use a common time frame for all shared resources. However, Velez and Maravelias (2013) proposed a discrete model that employs multiple time frames. One of the main challenges when setting up discrete models is the proper selection of the number of time periods that needs to be employed. A fine grid results to solutions of higher quality but in cost of larger less computationally efficient models. An advantage of discrete-time models is

their capability of monitoring inventory and backlog levels, material balances, as well as the availability and consumption of utilities without introducing nonlinearities. Moreover, time-dependent utility-pricing, holding and backlog costs can be linearly modelled, while integration with higher planning levels is straightforward (Maravelias and Sung 2009). Additionally, discrete-time formulations are superior to their continuous counterparts in terms of solution quality (Sundaramoorthy and Maravelias 2011). Nevertheless, discrete formulations result to very large, however tight, models, especially when small discretization of time is mandatory. 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 alleviate some of the computational issues associated with discrete-time models, since fewer time periods, thus variables, are required for the representation of the same scheduling problem. However, they are not necessarily more computationally efficient compared to their discrete counterparts. Finally, it should be mentioned, that few models that utilize multiple ways of representing time have been proposed, thus combining both the advantages of discrete- and continuous- time formulations (Kopanos, Puigjaner, and Maravelias 2011; Lee and Maravelias 2018, 2020).

1.2.3 Alternative MILP models for process scheduling

We already illustrated a classification of the various scheduling problems as well as the main modelling approaches that have been suggested in the last 30 years. A scheduling model is determined by both externally specified (problem class) and user selected (modelling approach) factors. On the one hand, the model should be suitable for the examined problem environment and the processing specifics of the facility under study, and on the other it should be developed in terms of the chosen modelling approach's characteristics. A given problem can be represented in multiple ways, however there is a significant relationship between these two aspects. In this subsection we will demonstrate the basic aspects of the mathematical models that have been proposed by the scientific community. More specifically, we present an overview of the models based on the problems they are used for. Further details on the different mathematical models for production scheduling can be found in the excellent review of Mendez et al. (2006).

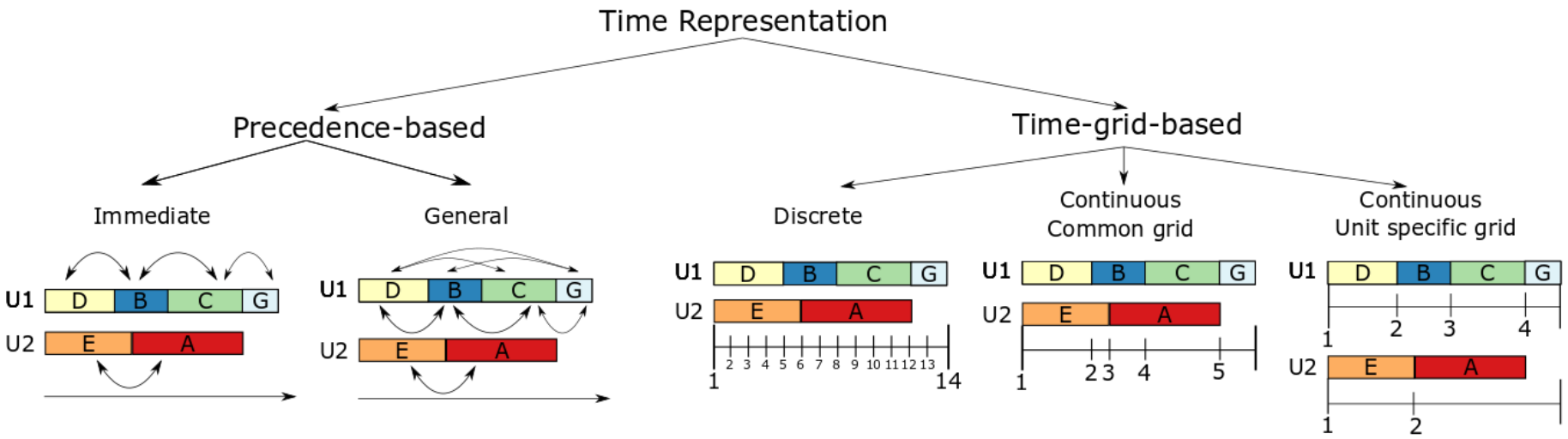

Figure 1.5: Categorization of modelling approaches based on time representation

1.2.3.1 Models for network production environments

In network environments batches do not maintain their identity, since mixing and splitting of batches is allowed. Therefore, the problem is presented utilizing 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. This necessitates the utilization of a time-grid based approach.

A plethora of modelling formulation emerged after the introduction of the discrete STN and RTN models. Reklaitis and Mockus (1995) were the first to propose a continuous-time formulation based on the STN formulation, exploiting its generality. A common resource grid is used, with the timing of the grid points ("event orders" in their terminology) determined by the optimization. The model is an 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 (1994, 1996) 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. An MINLP model ensues; this is solved using a local linearization procedure combined with what is effectively a column generation algorithm.

One of the major drawbacks of the first models developed according to the continuous STN and RTN mathematical frameworks was the large integrality gap. This deficiency was addressed by Schilling and Pantelides (1996). They modified the formulation of Zhang and Sargent (1996), simplifying it and improving its general solution characteristics, while 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.

Castro, Barbosa-Póvoa, and Matos (2001) proposed a relaxation of Schilling (1997), allowing tasks to last longer than the actual processing time. Consequently, their model is less degenerate, and less CPU time is required. Some of the co-authors further improved this formulation, allowing the optimization of continuous processes (Castro et al. 2004). A novel common-grid STN-continuous 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. The model of Sundaramoorthy and Karimi (2005) is another well-known continuous MILP model that introduced the idea of several balances (resource, time, masses etc.).

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 (Vin and Ierapetritou 2000; Janak, S.L., Lin, X., Floudas 2004; Shaik and Floudas 2009).

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 and Maravelias 2015). 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.

1.2.3.2 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 to address them. 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 impactful time-grid based models was suggested by Pinto and Grossmann (1995). They described an MILP model for the minimization of earliness of orders for a multiproduct plant with multiple equipment items at each stage. The interesting feature of the model is the representation of time, where two types of individual time grids are used: one for units and one for orders. Castro and Grossmann (2005) proposed a non-uniform time grid representation for the scheduling problem of multistage multiproduct plants. They tested their formulation for various objectives e.g., minimization of makespan, total cost and total earliness and compared it with other known formulations, concluding that a model's efficiency highly depends on the objective and the problem characteristics. The same authors extended their work with the consideration of sequence-dependent setup times (Castro et al. 2006).

Unlike to most of the other contributions, which propose continuous-time models, the work of Maravelias and co-workers thoroughly investigated the employment of discrete-time models in sequential environments. Sundaramoorthy, Maravelias, and Prasad (2009) suggested a discrete time model to incorporate utility constraints for the scheduling problem of multistage batch processes. Merchan, Lee, and Maravelias (2016) developed four novel formulations, two of them based on the STN and RTN representation and two more inspired by the Resource-Constrained Project Scheduling Problem (RCPSP). Moreover, the authors introduced tightening constraints and reformulations that allowed for significant computational enhancements. Recently, Lee and Maravelias (2017a) presented two new MIP 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 Process Systems Engineering (PSE) community (Gupta and Karimi 2003; Kopanos, Laı, and Puigjaner 2009). Numerous unit-specific immediate (Cerda, Henning, and Grossmann 1997), immediate (Méndez, Henning, and Cerdá 2000) and general precedence models (Méndez, Henning, and Cerdá 2001; Mendez and Cerdá 2004) have been proposed for scheduling problems in sequential environments. In initial studies the batches to be

scheduled was a problem data, however later contributions suggested models for the simultaneous batching and scheduling problem (Castro, Erdirik-Dogan, and Grossmann 2008).

1.2.4 Real-life Industrial Applications

As described in the previous section, a plethora of different mathematical models has been proposed to tackle the production scheduling problem. Except from solving literature problem examples, several researchers expressed a high interest for handling real-life industrial case studies. Numerous modelling approaches and methods can be found in the open literature, addressing a great variety of industrial process scheduling problems. We will present a literature review of contributions considering a variety of industrial sectors, e.g., chemical, pharmaceutical, petrochemical, steel, and consumer goods industries, and then we will focus on works studying the optimal scheduling problem of food industries. Notice that the presented literature review is limited on MILP-based approaches for the offline scheduling problem, excluding other solution methods (e.g., heuristic rules, metaheuristic algorithms etc.).

One of the main industrial sectors widely studied, considers chemical plants, where a variety of new products is produced via the chemical transformation of multiple raw materials. Floudas and Lin (2004) proposed a continuous time, event-based MILP scheduling model and a decomposition methodology, to solve large-scale industrial cases of multiproduct batch plants. Janak et al. (2006) extended the previous approach, by adapting intermediate due dates and other technical constraints. Westerlund et al. (2007) introduced a mixed discrete-continuous time formulation to tackle short-term and periodic scheduling problems of multi-product plants, including intermediate storage constraints, while in Velez, Merchan, and Maravelias (2015), a strategic planning tool was developed based on the proposed model and applied to an industrial plant, importing demand data from the plant's Enterprise Resource Planning (ERP) system. The introduced methods have been applied to a real case study from the Dow company (Nie et al. 2014).

A special subsector of the chemical plants is the pharmaceutical industry. Castro, Harjunkoski, and Grossmann (2009) presented a decomposition-based algorithm for tackling the high complexity of large-scale problems of multiproduct facilities. A case

study comprising of 50 production orders, 17 units and six stages is efficiently solved in less than one minute. The same pharmaceutical study case has been also considered by Kopanos et al. (2010). They proposed a decomposition-based solution strategy relying on two precedence-based MILP models in order to optimize different objectives, such as makespan, changeover-time and cost minimization. Stefansson et al. (2011) studied a large-scale industrial case study from a pharmaceutical company, including up to 73 products and 35 product families. Moniz et al. (2014) motivated by a real-world scheduling problem of a chemical-pharmaceutical industry, developed a case-specific discrete-time MILP scheduling model for batch plants. A representative industrial case including four products, nine shared processing units and 40 tasks, has been studied.

A special interest is expressed for the scheduling problem of oil refineries or petroleum industries. Zhang and Hua (2007) deployed a plant-wide multi-period planning model, aiming to the integration of the plant processes and the utility system, in order to reduce the energy consumption. The applicability of the approach is illustrated in a real study case that considers a refinery industry, located in South China. Shah, Sahay, and Ierapetritou (2015) motivated by a study case provided by Honeywell Process Solutions (HPS), considered an MILP based heuristic algorithm. The initial oil refinery problem is spatially decomposed into two subproblems, one considering the production and blending and the other the delivery of the finished products.

One of the main consumer goods group is the Fast Moving Consumer Goods (FMCG), which are characterized by frequent purchases, rapid consumption and low prices. 10 large-sized instances provided by The Procter & Gamble Company that consisted of up to 1391 operations have been solved within reasonable CPU times by Honkomp et al. (2000). Giannelos and Georgiadis (2003) developed an MILP model to address the scheduling problem in fast consumer goods manufacturing processes. The STN-based formulation was tested on a medium-sized industrial consumer goods manufacturing process, considering cases with up to 35 final products and five packing lines. Georgiadis et al. (2005) presented two different scheduling approaches, based on the RTN and the STN representations, respectively. A significant decrease in the operational cost was reported in a variety of problem instances provided by a large manufacturing company located in Greece. Elzakker et al. (2012) presented an algorithm based on a unit-specific, continuous time interval MILP model and ten industrial case studies are considered, as provided by Unilever. Optimal schedules have been generated

for problem instances of up to 73 batches of eight products allocated to six storage tanks and two packing lines within three minutes. Baumann and Trautmann (2014) proposed a hybrid method for large-scale, short-term scheduling problems that comprises of an MILP model and a heuristic algorithm. Elekidis, Corominas, and Georgiadis (2019) developed an immediate-general precedence-based model that focuses mainly on the packing stage. Various real-life case studies have been considered that include up to six packing lines and 130 final products.

Another important field of interest is the steel-making process industry. Various challenges arise, due to the large variety of final products, the complex process that take place and the volatile electricity prices. Biondi, Saliba, and Harjunkoski (2011) studied the scheduling problem of a hot rolling mill in a steel plant. Strict production constraints related to metallurgic production are taken into account. Li et al. (2012) considered the scheduling problem of steel making industries, focusing mainly on the steelmaking continuous casting process. A novel unit-specific event-based continuous-time MILP model is proposed, relied on material continuity and other technological requirements constraints in order to ensure the generation of feasible schedules. Yang et al. (2015) proposed an MILP mathematical formulation that optimizes the byproduct gas systems in steel plants. A representative case study from a steel plant in China has been considered and a significant reduction in the operation cost was noticed. Hadera et al. (2015) proposed a new general precedence MILP scheduling model adapting energy awareness. Wang et al. (2016) investigated the bi-objective single machine batch scheduling problem o f a real-world scheduling problem in a glass company located in Shanghai, China. An exact ε-constraint method is adapted to the MILP model in order to minimize the makespan and the total energy costs. Gajic et al. (2017) studied the integrated scheduling and electricity optimization problem of a hot rolling mill, taking also into account electricity costs and prices. An approach that combines MILP models and intelligent heuristics has been successfully implemented in the melt shop at Acciai Speciali Terni S.p.A.

A special interest has been expressed for the problem of trim loss minimization, mainly in the paper industry. Westerlund, Isaksson, and Harjunkoski (1998) studied the trim-loss problem of a Finnish paper-converting mill, resulting to waste savings of 2% of the turnover. Roslöf et al. (2000) developed various sophisticated heuristics that can be utilized in large scale industrial problems to provide feasible suboptimal solutions in

reasonable computational times. The real-life case studies provided by a Finnish paper mill included 61 scheduling jobs and a single processing unit. Giannelos and Georgiadis (2001) proposed a slot-based MILP scheduling model, which relied on a continuous time representation, to examine an industrial case study, provided by a paper mill company (Macedonian Paper Mills, S.A., Greece). Castro, Barbosa-Póvoa, and Matos (2003) proposed an MILP and an MINLP mathematical model, which were based on a continuous and a discrete time RTN representation and were applied to an industrial case study from a pulp mill plant located in Portugal.

1.2.4.1 Applications on Food industries

The scientific community has also shown significant interest for the scheduling of food industries. Common characteristics of food processing industrial facilities, such as intermediate due dates, shelf-life considerations and multiple mixed batch and continuous processing stages, substantially complicate the optimization of scheduling decisions. The above combined with market trends that enforce the gradual increase of the product portfolio, the demand profile (high variability-low volumes), and the multiple identical machines and shared resources, make the consideration of real-life industrial cases extremely challenging.

As the food industry focuses mainly on the production of perishable final products a make-to-stock production policy is not efficient, since the generation of high inventory levels should be avoided. A plethora of industrial case studies have been considered from various subsectors of the food industry. An immediate precedence-based MILP formulation for the packing stage of a brewery company was developed using a mixed discrete-continuous time representation in Kopanos, Puigjaner, and Maravelias (2011). The scheduling decisions are defined in a continuous manner, while material balances are expressed at each discrete time period to ensure the generation of feasible schedules. The idea of grouping the products into product families leads to significant reduction of the computational cost. Changeover times among sequential time periods are also taken into account. The industrial study case under consideration consists of eight processing units and 162 products grouped into 22 product families are produced. The generated solutions are better than the ones extracted by commercial tools. Baldo et al. (2014), motivated by a real study case from a Portuguese brewery, proposed a novel MILP-based

relax and a fix heuristic algorithm, for the integrated fermentation and packing problem. The time horizon is discretized in two subperiods. The first subperiod is scheduled in detail, as for the second subperiod only the main planning decisions, such as the inventory levels, are optimized. Small and big sized problem instances have been considered, with five filling lines and up to 40 products. Although a direct comparison with the company plan was not possible, good quality schedules were generated. Recently, Georgiadis et al. (2021) proposed an optimization-based solution strategy for the optimal production planning and scheduling of breweries. Their approach generated superior solutions compared to Baldo et al. (2014) and was successfully tested on a real-life case provided by a large Greek brewery. Koulouris, Misailidis, and Petrides (2021) discussed the concept of digital twin models and their application in the production scheduling problem of food industries. With the help of a large-scale brewery case study, the authors underlined the potential benefits from implementing a digital modeling approach. Simpson and Abakarov (2009) investigated the scheduling problem of food canneries focusing on the sterilization stage, allowing the possibility of the simultaneous sterilization of different products in the same retort. A graphic user interface, able to identify the nondominated simultaneous sterilization vectors, is connected to the proposed MILP model. Different cases are solved depicting a reduction of up to 25% in total plant operation time. Georgiadis et al. (2020) studied the scheduling problem of 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. Nearly optimal schedules of a large-scale problem instance, with 126 final products, have been generated in just 15 minutes. A study case of a real-world edible-oil deodorized industry is studied by Liu, Pinto, and Papageorgiou (2010). The plant is described as a single-stage multiproduct batch process. The final products are grouped into product families having the same due date. The proposed approaches rely on mixed discrete and continuous MILP mathematical formulations and classic TSP constraints. A real study case of 128 hours' time horizon of interest was studied. 70 orders of 30 different final products of seven groups of different release time have been scheduled. The new formulations are shown to be more efficient than previously proposed methods found in the literature. Polon et al. (2018) studied a sausage production industry aiming to the profit maximization by solving an MILP scheduling model for batch processes. The packing stage, which often constitutes the

main production bottleneck has not been considered. The plant operates in a single campaign mode and eight products are produced in total.

A special subsector of food industries is dairy manufacturing. Numerous products are produced, such as yoghurt, cheese and butter and distributed to customers worldwide. Touil, Echchatbi, and Charkaoui (2016) deployed an MILP model for a small multiproduct milk industry, located in Morocco, aiming at the minimization of makespan. The stages of homogenization, pasteurization and packing are scheduled for four final products, seven packing lines, two pasteurization units and one homogenizer. The production scheduling problem of an ice cream facility has been tackled by Kopanos, Puigjaner, and Georgiadis (2012). A real-life study case of eight final ice cream products, two packing lines and six aging vessels is addressed. 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. Doganis and Sarimveis (2007) solved the scheduling problem of a single yoghurt production line taking into account inventory, manpower and capacity restrictions. The model was tested using data from a yoghurt production line of a Greek dairy industry, where 18 products are produced. A novel mixed discrete-continuous MILP formulation is deployed by Kopanos, Puigjaner, and Georgiadis (2011) for the scheduling problem of a Greek yoghurt production facility. The idea of product families is adapted similarly to the other aforementioned works from the same authors. The packing stage is scheduled in detail, but mass balance constraints related to the production stage are also adapted, using a discrete time representation. 93 final products (grouped into 23 product families) are allocated in four packing lines. Novel resource constraints can adapt realistic limitations to various types of resources (e.g., manpower) and ensure the generation of feasible solutions. Based on a similar approach, the scheduling problem of another large scale Greek dairy industry has been studied (Georgiadis et al. 2019). A rolling horizon technique is embedded to reactively adjust the schedule in case of disturbances, like the cancellation or modification of orders, the sudden arrival of new orders or any digressions from the planned production. 158 final products (grouped into 44 product families) are allocated to six parallel packing lines, while the time horizon of interest is five days. A total cost decrease of 20% is achieved in comparison with the schedules

generated by the company. An integrated software tool with a user-friendly graphical interface has been developed to connect the proposed MILP model to the input data, located in excel files (parameter values such as changeover times etc.) and the ERP system (providing the demand values). As a result, optimal solutions can be generated automatically in less than 10 minutes. The integrated planning and scheduling problem of a small size Balkan type semi-continuous yoghurt facility, with 8 final product types, produced by three intermediates has been investigated by Sel, Bilgen, and Bloemhof-Ruwaard (2017). The evaluation of the proposed MILP approach has been utilized via a simulation model. 32 different scenarios were considered and a significant decrease in the total waste and makespan is achieved.

1.3 Supply chain optimization

Modern markets are characterized by increased competitiveness, while the current entrepreneurial environment is inherently dynamic, highly complex and uncertain. Therefore, the viability and later growth of companies requires their constant effort of developing a competitive advantage (Shadid 2018). To achieve that, a company should efficiently manage its whole supply chain, consisting of all entities, e.g., suppliers, manufacturing plants, warehouses, and customers, needed for the fulfilment of the requested demands. These entities are interconnected by material, information, and financial flows, which are represented by the known Supply Chain Network (SCN). Coordinating all necessary activities required to transform the raw materials into final products which are then delivered to the customers is called Supply Chain Management (SCM) (Stadtler et al. 2015). Enhancing these operations through the incorporation of optimization-based techniques is known as Supply Chain Optimization (SCO). The decisions related to SCM can be categorized into strategic, tactical, and operational based on the considered horizon. Strategic decisions are related to the long-term planning of the supply chain, i.e., the installation of new distribution centres. Medium-term planning decisions, such as, determining the inventory levels of a warehouse are tactical and lastly, the short-term decisions, like daily distribution of products, are included in the operational level. Recently, the scientific community has shown an increasing interest in the integration of the various decision levels, since it leads to a significant increase in the overall efficiency of the supply chain (Aguirre, Liu, and Papageorgiou 2018).

Acknowledging the positive effect optimal planning has on the efficiency of supply chains, the scientific community has extensively researched the topic, proposing a plethora of mathematical programming models (Mula et al. 2010). Liu and Papageorgiou (2013) defined the problem of integrated production, distribution, and capacity planning of global supply chains in terms of an MILP model. Multiple objectives (cost, flow time and lost sales) were investigated employing a lexicographic minimax and an ε-constraint approach. Ramos, Gomes, and Barbosa-Póvoa (2014) proposed a mathematical formulation and solution approach to support tactical and operational decisions in supply chains with reverse flows considering economic, environmental, and social objectives.

1.3.1 Healthcare supply chains

The healthcare supply chain considers the flow of medical products and services, in particular, pharmaceuticals, surgical or hygiene consumables, medical devises and vaccines, between several locations, such as, drug manufacturing plants, hospitals, clinics and patients (Imran, Kang, and Ramzan 2018). Information flow may involve, i) orders and processing data, ii) information on inventory levels, iii) pricing data and iv) the patient's medical information. Common financial flows are i) credit terms, ii) payment schedules and iii) consignment agreements.

Most contributions on healthcare supply chains consider problems of the pharmaceutical industry. This industry necessitates a complex set of processes involved in the discovery, development, and manufacturing of drugs. The supply chain of the pharmaceutical industry is like any other industry in the manufacturing phase. Despite the rich literature on SCO, only a small fraction of these studies addresses cases of the pharmaceutical sector. In one of the first significant contributions Papageorgiou, Rotstein, and Shah (2001) developed an MILP model in order to facilitate the strategic decision-making process for pharmaceutical industries. The suggested optimization approach is able to simultaneously select product development, introduction strategy, long-term capacity planning as well as investment strategy at multiple sites. Gatica, Papageorgiou, and Shah (2003) extended the previous work with the incorporation of uncertainty of clinical trials. Key issues regarding the long lead times of pharmaceutical products and the difficulties in balancing future capacity with anticipated demands considering the clinical trials uncertainty are underlined by Shah (2004). A generic

approach for planning and scheduling of supply chains with reverse flows is presented by Amaro and Barbosa-Póvoa (2008) and applied in a case study inspired by the pharmaceutical sector. Masoumi, Yu, and Nagurney (2012) consider the perishability of vaccines and the fact that they need to be refrigerated. The authors constructed an oligopoly model, that incorporates multiple firms competing in different markets, using variational inequality theory. Liu, Xie, and Garaix (2014) developed a tabu search metaheuristic that incorporates feasible and infeasible intra-route local search schemes to tackle a periodic vehicle routing problem for home healthcare logistics. Reverse flows in the pharmaceutical supply chain are investigated by Weraikat, Zanjani, and Lehoux (2016). More specifically, a decentralized negotiation process is proposed for the coordination needed to collect any unwanted medications at the customer zones. The integrated sustainable-resilient pharmaceutical supply chain under uncertainty was investigated by Zahiri, Zhuang, and Mohammadi (2017). The authors incorporated an MILP model with a possibilistic-stochastic programming approach to address uncertainty issues. Perishability issues were included in the optimization design problem of a pharmaceutical supply chain network in the work of Savadkoohi, Mousazadeh, and Torabi (2018). Jankauskas, Papageorgiou, and Farid (2019) solved the integrated capacity planning and scheduling problem of a biopharmaceutical industry. They proposed a genetic algorithm, whose hyperparameters are fine-tuned by a post-optimization procedure, based on the particle swarm optimization approach. The vehicle routing problem for the delivery of pharmaceutical products to healthcare facilities is addressed by Kramer, Cordeau, and Iori (2019). A multi-start iterated local search algorithm is employed to handle both realistic and artificial case studies. Recently, Sarkis et al. (2021) discussed the challenges and opportunities that emerge from the rise of personalised and complex drug production in both manufacturing and distribution.

Few recent contributions focused on supply chains of CAR T-cell therapies. These therapies require a complex and precise biomanufacturing process, which necessitates specialized staff, facilities, and equipment. The CAR T-cell SCN is highly complex, since blood must be first collected from the patient in a specialized treatment facility, which is then transferred to a manufacturing plant where the therapy is produced. Finally the patient must revisit the treatment facility so that the cell therapy is administered. Wang et al. (2018) proposed a multi-objective stochastic programming model for the optimal design of the CAR T-cell SCN and underlined the benefits achieved by the optimization

process. A review of the challenges associated with the CAR T-cell supply chains is presented by Papathanasiou et al. (2020). Recently, Karakostas et al. (2020) presented a novel modelling framework and an efficient solution approach to optimize the CAR T-cell supply chain. The authors proposed a patient-centric network structure, where the administration of CAR T-cell therapies is performed in local treatment facilities located close to patients' sites. They developed a General Variable Neighbourhood Search (VNS) algorithm, which was able to tackle realistically sized problems.

1.3.2 Vaccine supply chain

Immunization is one of the most successful and cost-effective public health interventions. Production, quality control and marketing authorization of vaccines is extremely complex due to three main reasons. Firstly, medical science advances resulted to highly sophisticated and effective vaccines that led to more complex manufacturing and testing procedures. Therefore, top quality facilities that can consistently produce quality vaccines are needed. Secondly, vaccine production utilizes globalized manufacturing chains to increase production capacity, Thirdly, strict regulatory requirements are imposed, to ensure public safety. Subsequently, the prolonged testing leaves less time for the distribution and administration of vaccines to patients. To deal with these complexities, the Vaccine Supply Chain (VSC) needs to be optimized in terms of structure, planning and operation, while considering the associated supply chain characteristics.

The VSC is characterized by two main phases, the manufacturing, and the distribution phase. A generic representation is provided in Figure 1.*6*. The manufacturing phase comprises of the first two steps (supply of raw materials and manufacturing of vaccines), while the rest belong to the distribution phase. Commonly the consumers are clustered, so the last two steps, customers, and consumers, can be considered to be the same step.

Managing the VSC brings many logistical questions. These are grouped into four components, i) what kind of vaccine should be used ii) how many doses should be produced and when, iii) who should be vaccinated and iv) how should the vaccines be distributed (Duijzer, van Jaarsveld, and Dekker 2018). Distributing the vaccines involves

design decisions e.g., related to the location and capacity of the various nodes (manufacturing plants, warehouses, and clinics), as well as, planning decisions, for example on the inventory levels and the routing decisions. Vaccines are perishable products, therefore, shelf-life issues must be considered. Furthermore, vaccines must always remain in low temperature conditions. Depending on the type of vaccine, they must remain refrigerated or frozen throughout their transportation and storage, making the VSC a temperature-controlled supply chain, or a cold chain as usually found in the literature. Keeping the cold chain uninterrupted throughout production, storage and distribution is critical to maintain the quality of the vaccines and ensure the effectiveness of the vaccination program. A special characteristic of the VSC that differentiates it from other supply chains is the need for mass distribution under high time pressure, especially in cases of sudden outbreaks.

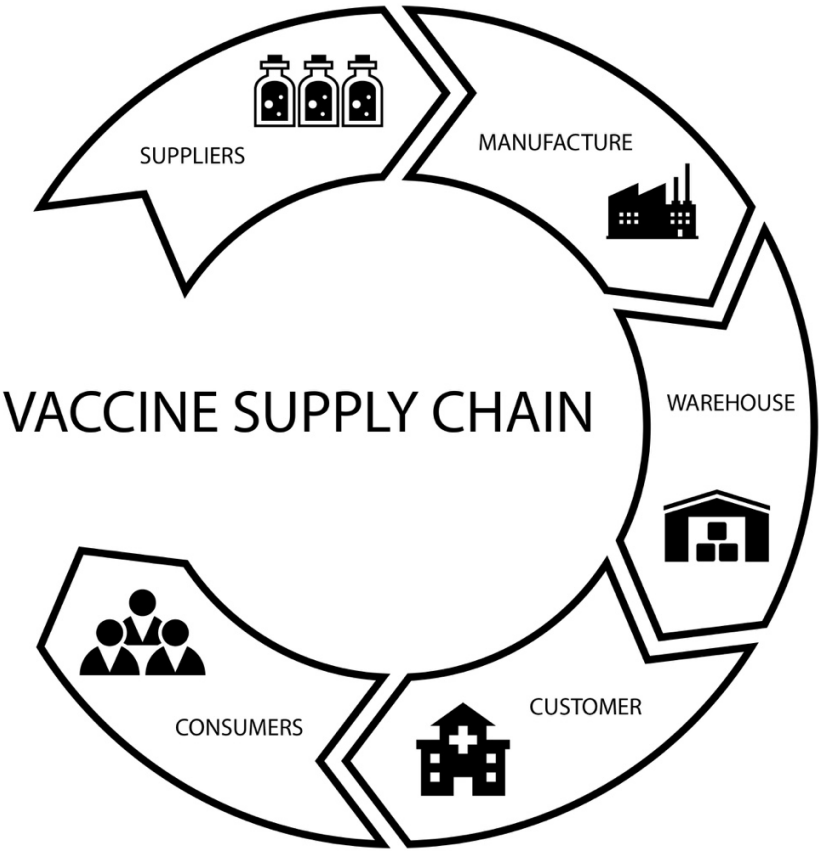

Figure 1.6: Vaccine supply chain structure (Ribeiro 2016)

In recent years, the scientific community has shown an increasing interest in VSCs. The distribution of thermosensitive vaccines is a challenging task especially for low - and middle-income countries, where the required infrastructure is unavailable. Therefore, Lee et al. (2012) developed a discrete-even simulation model for the Niger vaccine supply chain, to investigate the impact of making thermostable vaccines. They found out that making any vaccine thermostable strongly alleviates supply chain bottlenecks. Zaffran et al. (2013) state that designing products and packing in a way that meets the needs of developing countries will strengthen the logistics systems. Moreover, they underline the importance of information systems and internet connectivity for improving the decision-making process. Another paper proposes the integration of VSCs with other supply chains, like health commodities, to decrease costs (Yadav et al. 2014). This study provides a framework that decides where such integration offers significant benefits. However, integrating multiply supply chains poses a great challenge, since it further complicates any unique demand and supply characteristics. The design/redesign problem of VSC networks, especially in developing countries, has been considered in many contributions lately. Assi et al. (2013) generated a discrete-event simulation model of the Niger's supply chain to investigate the effect of removing the regional level. As a result, a remarkable increase in vaccine availability is reported. Two additional studies on the Benin's (Brown et al. 2014) and the Mozambique's supply chain (Lee et al. 2016) showed that redesigning significantly benefits the supply chain in both cost savings and vaccine accessibility. Two extensive literature reviews on the topic of VSCs were recently published. Lemmens et al. (2016) focus on models for the design of VSC networks, while Duijzer et al. (2018) review all issues related to the VSC from product selection to production, allocation and finally distribution of the vaccines.

Despite, the rich literature, only a handful of contributions consider the optimal planning of VSCs. This may be attributed to the fact that for traditional vaccines the most critical supply chain issues are related to the optimal design decisions in developing countries. Chen et al. (2014) developed the first planning model for a World Health Organization's Expanded Program on Immunization (WHO-EPI) distribution chain in developing countries. The proposed mathematical model can be used as a planning and evaluation tool, to understand bottlenecks and improve immunization rates. Another study proposed a multi-objective, multi-period model to address the simultaneous optimal design and planning of sustainable VSCs (de Carvalho, Ribeiro, and Barbosa-

Povoa 2019). The model is evaluated on a case study representing a European supply chain. Trade-offs between the sustainability dimensions considered (economic, environmental, and social) are highlighted. Recently, Yang (2020) investigated the optimal design and operation of WHO-EPI vaccine distribution chains. The author developed an MILP model and a disaggregation-merging technique to generate optimal solutions for real-world cases. Moreover, a systematic way to plan outreach operations with mobile clinics that will increase vaccine accessibility in regions of developing countries without access to direct clinic services is introduced.

The scientific community has not yet properly addressed the COVID-19 VSC. Recently, Kontoravdi et al. (2021) focused on the production phase of the vaccine. They emphasize the challenges of producing the required doses for the global vaccination campaign. The techno-economic feasibility of production is assessed for various RNA vaccines under development. The authors showed that the time required to meet global demand strongly depends on the RNA amount per dose, and the development of lower dose saRNA vaccines will significantly improve the production rates. The distribution phase of the COVID-19 supply chain has not been addressed so far. Only a few papers are published on the effect of the COVID-19 pandemic on other distribution supply chains (Rastegar et al. 2021). The COVID-19 distribution chain displays special characteristics that differentiate them from other VSCs. A prominent concern regarding the distribution of COVID-19 vaccines is the extreme temperature requirements during transportation and storage. The mRNA vaccines provided by Pfizer and Moderna must remain in deep-freeze conditions, -70^{o}C and -20^{o}C accordingly, while their lifetime in refrigerated conditions is limited. Especially in the case of the Pfizer vaccine, inefficient planning can lead to many valuable doses being wasted and to increased operational costs. These negative implications are further enhanced due to the enormous scale of the COVID-19 vaccination programs.

1.4 Thesis overview

This thesis is organized as follows:

Chapter 2 addresses the optimal production scheduling in multiproduct multistage plants that comprise of both batch and continuous processes. Two

modelling approaches are presented based on MILP frameworks. The first generates detailed optimal schedules for all processing stages involved, while the second proposes a novel aggregation technique that reduces the problem's complexity and allows its faster solution. At the end of the chapter, a computational analysis is performed to illustrate the efficiency of the proposed solution strategies.

Chapter 3 applies the methods presented in the previous chapter in a real-life large-scale industrial problem. More specifically, the optimal production scheduling of a food industrial process that includes two continuous preparation stages, a batch sterilization stage and finally a continuous packing stage, is studied. The process structure under consideration is commonly found in several industries. It is shown that both methods are able of providing near-optimal solutions leading to significant benefits in very low CPU times, compared to manually derived schedules generated by the production engineers.

Chapter 4 studies the integrated production planning and scheduling problem in breweries. The special characteristics that differentiate this production process are underlined. A new MILP model is developed to effectively address small- to medium-sized problem instances. To tackle larger problems, which are closer to the industrial reality, a two-step solution strategy is developed, relying on a decomposition and a re-optimization procedure. A computational analysis reveals that the newly proposed MILP model is superior to alternative approaches from the open literature. Furthermore, the developed solution strategy is successfully applied to case studies, which represent a real-life brewery.

Chapter 5 investigates the optimal short-term planning of the COVID-19 VSC. A novel MILP model is developed to address this problem. Multiple critical decisions such as inventory levels, transferred quantities and scheduling of vaccinations in the vaccination centres, are optimally taken. The solutions minimize the overall cost of the supply chain, including the cost due to doses that have been wasted. The proposed model is integrated in a solution strategy based on an aggregation and a divide-and-conquer approach to study complex problem instances including nation-wide supply chains. A case study simulating the Greek COVID-19 VSC is used to illustrate the applicability of the methods developed in this chapter.

Chapter 6 provides a synopsis of the research outcomes of this thesis and proposes possible future research directions.

Chapter 2

Optimal Production Scheduling of Multistage Multiproduct Process Industries

2.1 Introduction

In this chapter we address the optimal production scheduling problem in multistage multiproduct process industries. In particular, we focus on facilities that comprise of multiple mixed batch and continuous processes, a very common plant layout in various industrial processes, like pharmaceuticals, fast-moving consumer goods industries (FMCG) and especially food industries. Most of those industries usually consist of several processing stages that prepare the final products based on a given recipe, followed by a packing stage. These types of facilities are also known as make-and-pack. The stages that prepare the final products are batch, continuous or a mix of both, while the packing stage is a continuous process, thus resulting to a production procedure that consists of both batch and continuous processes. 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. This gap is even more evident when considering characteristics of real-life industrial problems, e.g., tight technical and logistical constraints, a large number of products and multiple processing lines.

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 mixed batch and continuous processes. Two optimization-based methods are introduced that approach differently the problem at hand. In the first approach, detailed production schedules are generated for all stages involved. The second follows a more aggregated approach that reduces the process into a purely

continuous one by indirectly including the batch process through a new set of feasibility constraints. Core of both solution strategies are new MILP models inspired by the precedence-based mathematical framework, while two different decomposition techniques are utilized to extend the applicability of the proposed methods into larger problem instances which are closer to the industrial reality.

2.2 Problem statement

A plant layout common in many make-and-pack industries is considered. The multistage multiproduct facility consists of both batch and continuous processes. In particular, the plant consists of three processing stages, i) a continuous process that transforms the raw materials into intermediate products based on a given recipe (preparation stage), ii) a sterilization process required to ensure the quality of the final products and iii) a packing stage necessary to bring the products into their final form. The sterilization process has been chosen as a general process since it is a very common procedure in many industries, thus extending the applicability of the study.

In total, two continuous stages are considered, with a batch processing stage (sterilization) in between. All stages comprise of multiple parallel machines. Each product must go through all processing stages. A product can be processed only by a subset of the available equipment in the continuous stages since the continuous lines of the preparation and packing stages have different capabilities. In contrast all sterilization chambers are identical, therefore a product may be processed in any of them. It is assumed that the intermediate products in the output of the preparation stage are grouped into carts to be transferred to the sterilization chambers. The implementation of other more general grouping methods can be done in a straightforward manner. To ensure the safety and quality of the final products, a maximum waiting time is allowed between the preparation and the sterilization stage. This is a rather low waiting time that incommodes the computational speed of the proposed method, however incorporating it is critical to ensure the feasibility of the generated production schedules. A single campaign policy is favored by most industries, therefore order splitting is not considered. A product order is continuously processed in a single line in the continuous stages of the facility. However, most product orders are larger than the capacity of the sterilization

chambers, therefore, they are divided into several batches. To improve the efficiency of the plant these can be processed by multiple sterilizers. Conclusively, a product order is split into numerous batches, whose associated lots are processed continuously in a single line in the continuous stages but can be processed by multiple sterilizers in the batch stage. This production process poses difficult synchronization issues that must be considered to significantly improve the efficiency of the plant.

The problem under study can be formally stated as follows.

Given:

- A known scheduling horizon H divided into a set to time periods $n \in N$.
- A set of continuous processing stages $s \in S$.
- A set of continuous processing lines $j \in J$.
- The multidimensional set $JS_{j,s}$ describing whether a line j belongs in a processing stage s.
- A set of products $p \in P$ to be processed within the scheduling horizon, with all production related parameters, such as, demand, due date, processing rate in the continuous lines $\tau_{j,p}^{rate}$ and sterilization time τ_p^{ster}.
- The multidimensional set $JP_{j,p}$ denoting which lines can process each product p.
- A set of product batches $b \in B$. This set is required since the order-sizes are usually larger than the capacity of the sterilization chambers.
- The multidimensional set $PB_{p,b}$ denoting which batches b belong to a product p.
- A changeover task required in any continuous line j whenever the production is changed between two different products. Every changeover operation requires a specific time $\gamma_{j,p,p\prime}$.
- The parameters related to the sterilization stage, in particular the capacity of each cart for every product p, (χ_p) the number of carts that fill up a sterilization chamber (χ^{ST}) and the number of available sterilizers in the facility (v^{ST}).

Determine:

- The allocation of products into lines in every stage.

- The sequencing between products in each line.
- The starting and completion time for the processing of each product p in each stage s.

, in order to minimize the production makespan or the total changeover time.

This problem definition is more general and encompasses both mathematical frameworks presented in the next section. Both tackle the optimal production scheduling problem of multistage multiproduct facilities with mixed batch and continuous processes, however from a different point of view. The special characteristics of each approach that add on top of the general problem statement presented above are provided in the beginning of the related subsection.

2.3 Mathematical frameworks

2.3.1 Approach A: Detailed production scheduling of mixed batch and continuous processes

In this first modelling approach, all processing stages are modelled explicitly. Detailed decisions for all stages involved are specifically provided. The scheduling horizon is divided into n daily time periods.

In particular, we determine:

- The allocation of products into units in every stage s and time period n $Y_{p,s,j,n}$ and the allocation of all batches b of each product p in the sterilization stage $\bar{Y}_{p,b,j,n}$.
- The sequencing between products in each line and stage, which is expressed by general precedence variables $X_{p,p',j,n}$.
- The starting $L_{p,b,s,n}$ and completion time $C_{p,b,s,n}$ for the processing of each product p and batch b in each stage s and time period n.

The developed MILP-based solution strategy consists of free main pillars (Figure *2.1*):

- A pre-processing algorithm that translates production orders into batches presented in subchapter 2.3.1.1.
- The mathematical model describing the scheduling problem.

- A decomposition technique that splits the initial problem into tractable easily solvable subproblems.

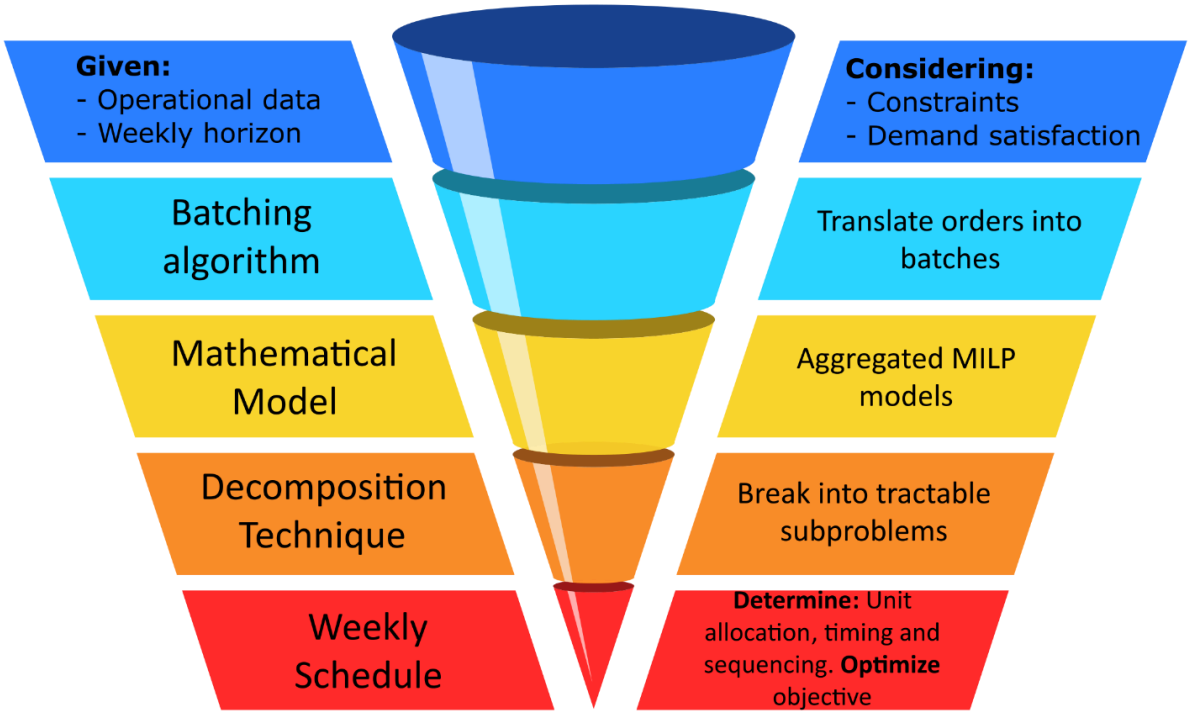

Figure 2.1: Illustrative description of developed solution strategy

2.3.1.1 Batching algorithm

The goal of this batching algorithm is to convert the product orders into batches in the sterilization stage to fully satisfy the given demand. Moreover, in this step, we calculate the processing time required for the first batch in the first continuous stage and the last batch in the packing stage. These parameters are later required in the mathematical models. In many industries the industrial practice imposes the operation of the intermediate batch processes to their maximum capacity. The maximum utilization of the sterilization stage allows for high production levels while ensuring minimization of changeovers between products. Thus, the batching problem can be solved a priori. After the completion of the previous process, the intermediate products are loaded in carts that are pushed into the sterilization chambers. All product orders are at least the size of one full batch, but the capacity of the sterilizers may not be an exact divisor of the order size. Therefore, the last batch of any order may be smaller than the rest. To calculate the necessary batch-related parameters, we employ the following equations:

$$n_p^c = \frac{\zeta_p}{\chi_p} \tag{2.1}$$

$$n_p^b = \left\lceil \frac{n_p^c}{\chi^{ST}} \right\rceil \tag{2.2}$$

$$n_p^{Full} = \left\lfloor \frac{n_p^c}{\chi^{ST}} \right\rfloor \tag{2.3}$$

$$q_p^{FB} = \chi_p \cdot \chi^{ST} \tag{2.4}$$

$$q_p^{LB} = \begin{cases} \chi_p \cdot \chi^{ST} & ,when\ n_p^b = n_p^{Full} \\ (n_p^c - n_p^{FB} \cdot \chi^{ST}) \cdot \chi_p & ,when\ n_p^b \neq n_p^{Full} \end{cases} \tag{2.5}$$

$$\tau_{j,p}^{FB} = \frac{q_p^{FB}}{\tau_{j,p}^{rate}} \quad \forall j \in (JP_{j,p} \cap JS_{j,s}),\ s \neq 2 \tag{2.6}$$

$$\tau_{j,p}^{LB} = \frac{q_p^{LB}}{\tau_{j,p}^{rate}} \quad \forall j \in (JP_{j,p} \cap JS_{j,s}),\ s \neq 2 \tag{2.7}$$

In equation (2.1) the total number of required carts for each product is calculated, by dividing product demand ζ_p over the capacity of the carts χ_p, which depends on the product's size. Equation (2.2) defines the minimum number of batches required to satisfy demand (n_p^b), by dividing the calculated number of carts over the number of carts that fill each batch processing equipment χ^{ST}. Since every batch equipment has the same specifications, this number is constant. However, the total number of carts for each product may not be exactly divided by this number. Therefore, in equation (2.3) we also define n_p^{Full}, which is the number of fully utilized batches. Based on that information, the quantity processed in the first and last batch is calculated. The quantity of the first batch of each product order is always equal to the capacity of each cart multiplied by the number of carts that fill a batch processing equipment, as shown in equation (2.4). However, the capacity of the last batch depends on whether it is a full batch or a batch of reduced size (2.5). Finally, the required processing time for the first batch $\tau_{j,p}^{FB}$ and the

last batch of each product in every available continuous line $\tau_{j,p}^{LB}$, is calculated using equations (2.6) and (2.7) accordingly.

In Figure 2.2 the flowchart of the batching algorithm is illustrated.

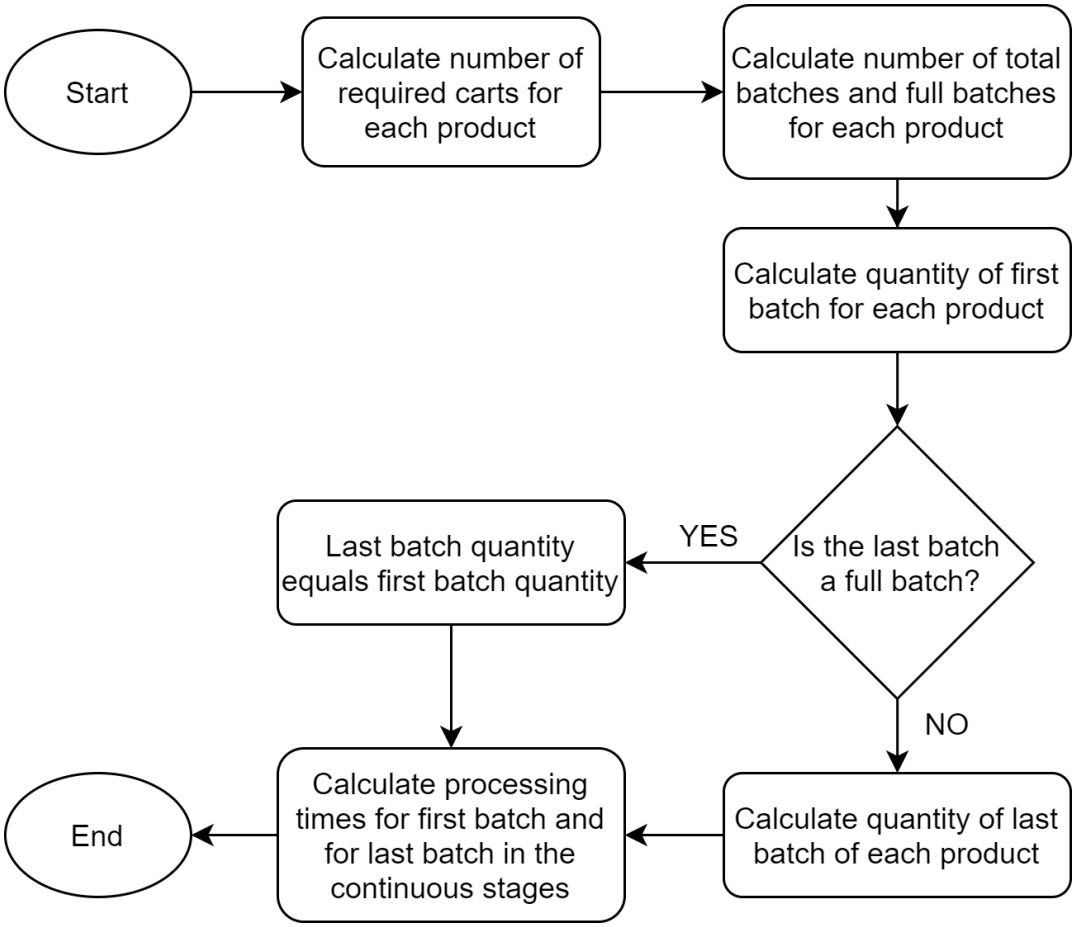

Figure 2.2: Flowchart of batching algorithm

To better clarify the meaning of these parameters, let us consider an example of an order with a size of 120000 units of a specific product, with a cart capacity of 5000 units. In that case, the total amount of required carts is:

$$n_p^c = \frac{\zeta_p}{\chi_p} = \frac{120000}{5000} = 24$$

The number of full batches and total batches are calculated as follows:

$$n_p^{Full} = \left\lfloor \frac{n_p^c}{\chi^{ST}} \right\rfloor = \left\lfloor \frac{24}{9} \right\rfloor = 2$$

$$n_p^b = \left\lceil \frac{n_p^c}{\chi^{ST}} \right\rceil = \left\lceil \frac{24}{9} \right\rceil = 3$$

Furthermore, let us assume that this product can only be processed by one line in the first continuous stage and one in the packing stage, with a rate of 45000 units/hour. Therefore, the considered processing times will be

$$\tau_{j,p}^{FB} = \frac{q_p^{FB}}{\tau_{j,p}^{rate}} = \frac{\chi_p \cdot \chi^{ST}}{\tau_{j,p}^{rate}} = \frac{5000 \cdot 9}{45000} = 1 \ hour$$

for the first batch and

$$\tau_{j,p}^{LB} = \frac{q_p^{LB}}{\tau_{j,p}^{rate}} = \frac{(n_p^c - n_p^{FB} \cdot \chi^{ST}) \cdot \chi_p}{\tau_{j,p}^{rate}} = \frac{5000 \cdot (24 - 9 \cdot 2)}{45000} = 40 \, minutes$$

for the last batch in the continuous stages.

2.3.1.2 MILP model

The proposed MILP model is inspired by the general precedence framework. A daily discretization of the considered horizon is employed. Moreover, a cyclic heuristic is implemented for the sterilization stage, to reduce the problem's combinatorial complexity. The daily demand must be satisfied within the specified time period, so backlogs are not allowed. The batches and associated lots in the continuous processes, calculated from the batching algorithm, must be completed within the given time period. It is assumed that the plant shuts off at the end of each time period for maintenance purposes, so all production processes must be completed within one time period. For example, a product order cannot undergo the preparation and the sterilization stage in time period *n* and the packing process in time period *n+1*. The constraints of the developed model are presented below and are categorized based on the type of decisions that they include.

Allocation constraints. Constraints (2.8) – (2.10) impose the allocation constraints of the model, introducing the binary variables $Y_{p,s,j,n}$, $\bar{Y}_{p,b,j,n}$, and $Y_{p,j,n}^{F}$. To comprehend these constraints, we must introduce the subset $SB_{p,n}$. This includes all products that

consist of a single batch. In those cases, it is not required to specify an additional index *b* in the associated allocation variable. More specifically, constraints (2.8) pose the allocation constraints for the continuous stages ($s \neq 2$), but also for the products consisting of a single batch in the sterilization stage. Constraints (2.9) focus on the sterilization stage and the products that comprise of multiple batches and guarantee that all product batches *p, b* to be scheduled on day *n* will be processed by exactly one sterilizer. Finally, constrains (2.10) are necessary for the cyclic heuristic that follows. Variable $Y^F_{p,j,n}$ denotes the allocation of the first batch of product *p* in the sterilization stage. The constraints ensure that the first batch of every product must be processed by exactly one sterilizer.

$$\sum_{j\in(JS_{j,s}\cap JP_{j,p})} Y_{p,s,j,n} = 1 \qquad \forall p \in I^{in}_p, n \in I^{In}_n, (s \neq 2 \cup (s = 2 \cap p \in SB_{p,n})) \qquad (2.8)$$

$$\sum_{j\in(JS_{j,'ST'}\cap JP_{j,p})} \overline{Y}_{p,b,j,n} = 1 \qquad \forall p \in I^{in}_p, p \notin SB_{p,n}, b \in PB_{p,b,n}, n \in I^{In}_n \qquad (2.9)$$

$$\sum_{j\in(JS_{j,'ST'}\cap JP_{j,p})} Y^F_{p,j,n} = 1 \qquad \forall p \in I^{in}_p, p \notin SB_{p,n}, n \in I^{In}_n \qquad (2.10)$$

Cyclic allocation heuristic. A great increase in the problems computational complexity originates from the flexibility of production in the sterilization process. The products can be processed in any of the available sterilizers, which often are many. Therefore, the solver used for the developed MILP model will have to examine numerous nodes, which result to same quality solutions. Since the sterilizers have the same characteristics, it does not make any difference in the schedule's quality whether a product batch is processed in sterilizer 1 or sterilizer 2 etc. Therefore, an algorithm is introduced that heuristically allocates the product batches in the sterilization chambers. This algorithm is inspired by Kopanos, Puigjaner, and Georgiadis (2012) and states that the only decisions that must be optimally taken by the model, are the allocation decisions of the first batch of each product $Y^F_{p,j,n}$, the rest of the allocation decisions in the sterilization stage can be heuristically extracted without affecting the solution quality. The heuristic specifies that every next batch of a product will be processed by the next indexed sterilizer. For example, if the first batch of a product is processed in sterilizer *ST_1*, then the next will be processed in *ST_2*, the next in *ST_3* and so on. To further reduce the model's size, we can specify the "size" of this cycle, or the number of units used for

the sterilization process of the order's batches. To define this number, we assume that an uninterrupted process is desired in the packing stage. Usually, the sterilization stage is the slowest process of the facility. Since a single campaign policy is required in the packing stage, an uninterrupted processing procedure requires the employment of multiple sterilizers. The number of sterilizers used in the cyclic heuristic for a product is calculated as the minimum number of sterilizers that ensure an uninterrupted process in the packing stage. For example, if the packing process lasts 1 hour for a product, while the sterilization process lasts 2 hours for the same product, then 2 sterilizers will be used in the cyclic heuristics of this product. Alternatively, if the sterilization process lasts 2.5 hours, then 3 sterilizers will be employed in the heuristic. Figure *2.3* provides an illustrative example of the proposed heuristic. Let us assume that a product order consists of 10 batches and that the heuristic employs 3 sterilizers. The optimization model generates a solution which states that the first batch of product *P1* must be processed in sterilizer *ST_1*. The heuristic decides on the rest of the allocation variables as shown, without burdening the optimization procedure. As a result, a significant reduction in CPU times is reported.

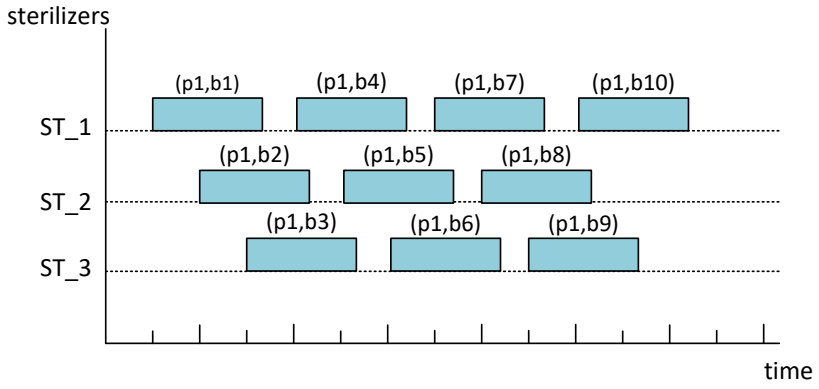

Figure 2.3: Description of cyclic heuristic in the sterilization stage

Constraints (2.11) – (2.13) imprint mathematically the cyclic heuristic described above. Subset $Cyc_{p,b,n}$ is introduced, which includes all batches that utilize the same sterilizer with the first batch. In the example presented in Figure 2.3, $Cyc_{p,b,n} = \{(p_1, b_1, n), (p_1, b_4, n), (p_1, b_7, n), (p_1, b_{10}, n)\}$. First, constraints (2.11) define that the sterilizer used for processing the first batch of a product p in time period n, is the same with the sterilizer used for the rest of the batches in subset $Cyc_{p,b,n}$. The next two

constraint sets focus on the rest of the batches $b \notin Cyc_{p,b,n}$. Constraints (2.12) state that if a batch b is processed in sterilizer j, then the next batch $b+1$ will be processed in sterilizer $j+1$. Finally, constraints (2.13) examine the special case, where batch b is processed in the last available sterilizer LST_j. In that case, the next batch $b+1$ must be processed in the first sterilizer FST_j.

$$Y^F_{p,j,n} = \bar{Y}_{p,b,j,n} \qquad \forall p \in I^{in}_p, p \notin SB_{p,n}, n \in I^{In}_n, j \in JS_{j,'ST''}, b \in Cyc_{p,b,n} \qquad (2.11)$$

$$\bar{Y}_{p,b,j,n} = \bar{Y}_{p,b',j',n} \qquad \forall p \in I^{in}_p, p \notin SB_{p,n}, n \in I^{In}_n, b \in PB_{p,b,n}, b' \in PB_{p,b',n}, b' = b+1, b' \notin Cyc_{p,b',n}, j, j' \in JS_{j,'ST'}, j \notin LST_j, j' = j+1 \qquad (2.12)$$

$$\bar{Y}_{p,b,j,n} = \bar{Y}_{p,b',j',n} \qquad \forall p \in I^{in}_p, p \notin SB_{p,n}, n \in I^{In}_n, b \in PB_{p,b,n}, b' \in PB_{p,b',n}, b' = b+1, b' \notin Cyc_{p,b',n}, j \in LST_j, j' = FST_j \qquad (2.13)$$

Timing constraints. Constraints (2.14) impose the timing constraints in the sterilization stage. They state that the completion of the sterilization process for every product batch to be scheduled in a day $(C_{p,b,s,n})$ is equal to the starting time of the task $(L_{p,b,s,n})$ plus the required sterilization time (τ^{ster}_p). Similarly, constraints (2.15) define the completion time for the continuous stages. Synchronizing the stages necessitates the introduction of constraints (2.16). The continuous variable $W_{p,b,s,n}$ defines the waiting time between each stage.

$$L_{p,b,s,n} + t^{ster}_p = C_{p,b,s,n} \qquad \forall p \in I^{in}_p, n \in I^{In}_n, b \in PB_{p,b,n}, s \in ST_s \qquad (2.14)$$

$$L_{p,b,s,n} + \sum_{j \in JS_{j,s} \cap JP_{j,p}} (t^{proc}_{p,b,j,n} \cdot Y_{p,s,j,n}) = C_{p,b,s,n} \qquad \forall p \in I^{in}_p, n \in I^{In}_n, b \in PB_{p,b,n}, s \in CS_s \qquad (2.15)$$

$$C_{p,b,s,n} + W_{p,b,s,n} = L_{p,b,s+1,n} \qquad \forall p \in I^{in}_p, n \in I^{In}_n, b \in PB_{p,b,n}, s < 3 \qquad (2.16)$$

Sequencing constraints. Constraints (2.17) and (2.18) guarantee the proper timing between the batches of the same product. The first focuses on the continuous stages while the second on the sterilization stage. In particular, (2.17) respects the single campaign policy by stating that a batch b of product p finishes before starting the next batch of the same product. Expressing this constraint for the sterilization stage is slightly more complicated due to the cyclic heuristic. More specifically, the sterilization process for

batch b of product p must be completed prior to the start of the sterilization process for batch $b' = b + \kappa_{p,n}$, where $\kappa_{p,n}$ denotes the number of sterilization chambers used for the product based on the cyclic heuristic (2.18). The sequencing constraints between batches of different products are given in constraints (2.19) - (2.22). The first two are related with the continuous stages for all products and the sterilization stage for products consisting of a single batch, while the next two are related with the sterilization stage for the rest of the products. A general precedence variable $X_{p,p',s,n}$ is introduced. When it is active, it denotes that product *p'* follows product *p* in stage *s* and time period *n*. Constraints (2.19) state that if a product *p* is processed prior to *p'* in stage *s* and period *n* ($X_{p,p',s,n} = 1$) and both products are processed in the same unit ($Y_{p,s,j,n} = Y_{p',s,j,n} = 1$), then the starting time of the first batch of product *p'* must be greater than the completion time of the last batch of product *p* ($PBL_{p,b,n}$) plus any required changeover time ($\gamma_{j,p,p'}$). Constraints (2.21) pose the same but for the sterilization stage and for products with multiple batches. Here the sequencing constraints are imposed on sets $FCB_{p,b,n}$ and $LCB_{p,b,n}$. These denote the first $\kappa_{p,n}$ and last $\kappa_{p,n}$ batches of the product, accordingly, as defined by the cyclic heuristic. Notice that we choose to define the sequencing constraints between batches of different products only for the first and last batches of the products. The sequencing of the rest of the batches between different products are irrelevant, due to constraints (2.17) and (2.18) and would only increase the size of the model without providing any useful information. As a result, the model's size remains as small as possible allowing for a faster solution. Constraints are defined only for *p<p'*, a known technique used in the general precedence framework for model size reduction, therefore the complementary constraints (2.20) and (2.22) are required.

$$C_{p,b,s,n} \le L_{p,b+1,s,n} \qquad \forall p \in I_p^{in}, n \in I_n^{In}, b \in PB_{p,b,n}, s \ne 2 \qquad (2.17)$$

$$C_{p,b,s,n} \le L_{p,b',s,n} \qquad \begin{array}{l} \forall p \in I_p^{in}, p \notin SB_{p,n}, n \in I_n^{In}, b \in PB_{p,b,n}, \\ b' \in PB_{p,b',n}, b' = b + \kappa_{p,n}, s = 2 \end{array} \qquad (2.18)$$

$$\begin{array}{l} L_{p',b',s,n} \ge C_{p,b,s,n} + \gamma_{j,p,p'} - M \cdot (1 - X_{p,p',s,n}) \\ -M \cdot (2 - Y_{p,s,j,n} - Y_{p',s,j,n}) \end{array} \qquad \begin{array}{l} \forall p \in I_p^{in}, p' \in I_{p'}^{in}, p < p', n \in I_n^{In}, \\ b \in PBL_{p,b,n}, b' \in PB_{p',b',n}, b' = 1, \\ (s \ne 2 \cup (s = 2 \cap p \in SB_{p,n} \cap \\ p \in SB_{p',n})), j \in (JPP_{j,p,p'} \cap JS_{j,s}) \end{array} \qquad (2.19)$$

$$L_{p,b,s,n} \geq C_{p',b',s,n} + \gamma_{j,p',p} - M \cdot X_{p,p',s,n} - M \cdot (2 - Y_{p,s,j,n} - Y_{p',s,j,n}) \quad \forall p \in I_p^{in}, p' \in I_{p'}^{in}, p < p', n \in I_n^{In}, b' \in PBL_{p',b',n}, b \in PB_{p,b,n}, b = 1, (s \neq 2 \cup (s = 2 \cap p \in SB_p \cap p' \in SB_{p'}), j \in (JPP_{j,p,p'} \cap JS_{j,s}) \quad (2.20)$$

$$L_{p',b',s,n} \geq \underline{C}_{p,b,s,n} - \underline{M} \cdot (1 - \cdot X_{p,p',s,n}) - M \cdot (2 - \underline{Y}_{p,b,j,n} - \underline{Y}_{p',b',j,n}) \quad \forall p \in I_p^{in}, p' \in I_{p'}^{in}, p < p', n \in I_n^{In}, b \in LCB_{p,b,n}, b' \in FCB_{p',b',n}, s = 2, p \notin SB_p, p' \notin SB_{p'}, j \in JS_{j,s} \quad (2.21)$$

$$L_{p,b,s,n} \geq \underline{C}_{p',b',s,n} - \underline{M} \cdot X_{p,p',s,n} - M \cdot (2 - \underline{Y}_{p,b,j,n} - \underline{Y}_{p',b,j,n}) \quad \forall p \in I_p^{in}, p' \in I_{p'}^{in}, p < p', n \in I_n^{In}, b \in FCB_{p,b,n}, b' \in LCB_{p',b',n}, s = 2, p \notin SB_p, p' \notin SB_{p'}, j \in JS_{j,s} \quad (2.22)$$

Quality constraints. Constraint set (2.23) enforces the waiting time between the preparation and the sterilization stage to be less than a specific limit Q_p. This limit ensures the safety and quality of the final product.

$$L_{p,b,s+1,n} - C_{p,b,s,n} \leq Q_p \quad \forall p \in I_p^{in}, n \in I_n^{In}, b \in PB_{p,b,n}, s = 1 \quad (2.23)$$

Objective. Goal of the MILP model is the minimization of the total production makespan C^{max}, which is expressed by the following constraints:

$$C^{max} \geq C_{p,b,j,n} \quad \forall p \in I_p^{in}, n \in I_n^{In}, b \in PBL_{p,b,n}, j \in JS_{j,s}, s = 3 \quad (2.24)$$

2.3.1.3 Decomposition strategy

The complexity of the examined plant is such that an exact method cannot solve the scheduling problem in a reasonable CPU time. Therefore, a two-step decomposition algorithm is employed to split the initial problem into several tractable subproblems. First, the weekly scheduling problem is decomposed in a temporal manner into *n* daily scheduling subproblems, depending on the number of time periods in the considered horizon. Then, an order-based decomposition is utilized to solve the daily scheduling problem for a specific number of products in each iteration. Figure 2.4 illustrates the

flowchart of the proposed solution strategy. At first the batching subproblem is solved to translate the product orders into batches. Afterwards, the number of orders to be scheduled in each iteration are set. Then, the MILP model is solved for the specified subproblem area (day and number of products) and all binary variables (unit allocation, sequencing) are fixed. In contrast, the continuous variables are reoptimized after every iteration, thus increasing the flexibility of the solution strategy. When all orders are scheduled for a given day, all variables are fixed, and the algorithm continues to the next day. Finally, when all days are considered, the complete optimal schedule is generated.

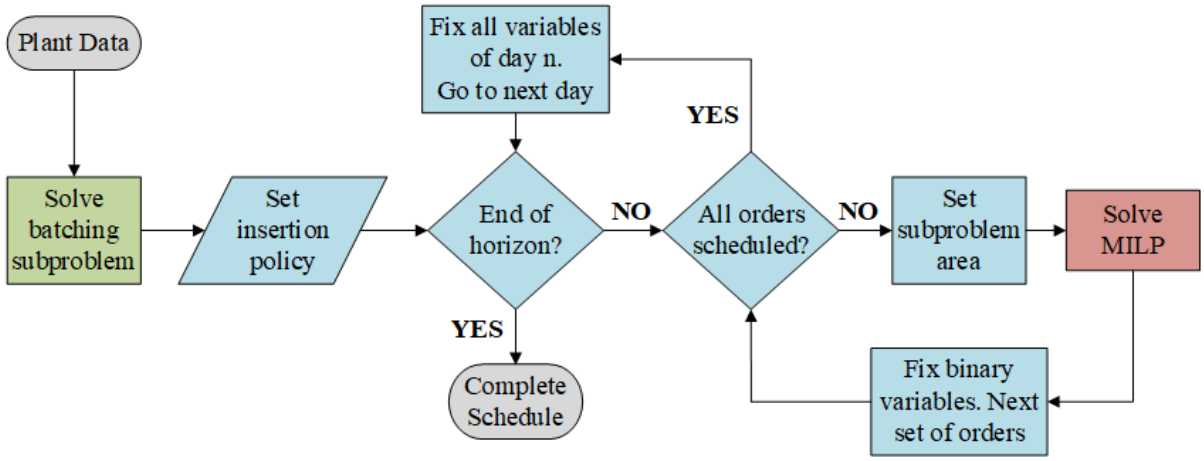

Figure 2.4: Flowchart of solution strategy implementing a two-step decomposition algorithm

2.3.2 Approach B: Aggregated production scheduling of mixed batch and continuous processes

In the previous approach we have stressed the importance of efficiently modelling the sterilization stage, due to the combinatorial complexity it introduces to the model. Therefore, a cyclic heuristic has been proposed to reduce the involved constraints and decision variables. In this section we present an alternative approach that further reduces the items involved with the sterilization stage. In fact, this stage is completely omitted from the optimization model with the introduction of a novel aggregated approach that however incorporates all significant considerations related to the sterilization stage. Conclusively, more efficient models are generated that provide faster, feasible solutions, which however do not include detailed decisions for the sterilization stage. The improved efficiency allows for the consideration of more complicated objectives, e.g., changeover

minimization, impossible to be studied in reasonable CPU times using the first approach. Moreover, a unified scheduling horizon is employed that increases the production flexibility of the plant, since the production process of an order can last multiple days. This approach also includes a useful extension for many industries. Often equipment is shared between processing lines, therefore an additional set of constraints is included that considers the case where some packing lines may share the same labelling machine. Of course, this can be easily extended to any type of shared resource.

Two MILP models are presented to efficiently address the scheduling problem of a multistage multiproduct industrial facility. The first is based on the general precedence framework, while the second is inspired by the unit-specific general precedence formulation (Kopanos et al. 2009). Specific characteristics of the production are exploited to formulate aggregated models, that significantly simplify the problem. However, the combinatorial complexity of the examined problem is still prohibitive for the straightforward application of these models in large-scale problem instances using any known solver, like CPLEX. Therefore, we also investigate a decomposition strategy, that allows for the fast generation of feasible schedules.

2.3.2.1 Conceptual model design

Using MILP-based frameworks to model all processing stages together leads to problems that are intractable with the current computational power. This is mostly due to the large number of involved items, in particular, processing stages, units and products. A common way of addressing complicated problems using low computational times is the simplification of the overall process by solely focusing on the scheduling of a specific stage that constitutes a production bottleneck. Unfortunately, such an assumption cannot be done in this problem since the production bottleneck shifts according to the demand profile. Therefore, other ways of reducing the problem's complexity, however without generating infeasible schedules, must be investigated. One of the main sources of increased combinatorial complexity is the batch process, since in contrast to the rest of the processing stages, each product can be processed by any of the available machines. Unfortunately, we cannot neglect it entirely. However, it is noticed that the scheduling decisions related to the batch stage, do not affect the quality of the final schedule. This occurs, since all batch processing machines are identical and as such no sequence-

dependent setups exist. Therefore, the inclusion of the batch stage is a potential source of degenerate solutions. For instance, let us consider a simple case, in which only two sterilizers *ST1* and *ST2* exist and two products *P1* and *P2* are to be scheduled. Note that alternate allocation decisions i.e. {*P1* → *ST1; P2* → *ST2*} or {*P1* → *ST2; P2* → *ST1*} are equivalent, since the batch time for both products is the same using any machine. The same holds for the sequencing decisions. Since no changeovers exist, it does not matter whether *P1* is processed before *P2* or vice versa. Based on this observation, the batch processing equipment can be viewed as a finite renewable resource, similar to e.g., manpower. Therefore, while it is not explicitly modelled, it is indirectly incorporated in the model. Feasibility constraints related to the availability of time and units are imposed. These constraints ensure that: a) enough time between the continuous processes of a product exists for the required batch process and b) that at any time point there is available equipment to complete the batch process. Consequently, the process is reduced to a purely continuous one, consisting of two stages and a number of feasibility constraints for the batch stage in-between. The use of this aggregated approach significantly reduces the combinatorial complexity of the problem at hand.

To exploit the benefits of both time representation approaches, a mixed discrete-continuous time representation is used. The size of the problem necessitates the employment of a continuous-time representation, since fewer variables are required and smaller, easier solvable, models are generated. However, a known disadvantage of this approach is its inability to efficiently monitor the consumption and/or availability of resources (Floudas and Lin 2004). This is an extremely important feature that must be included in the model since batch equipment is described as a renewable resource. Therefore, a discrete-time grid is employed on top of the continuous one. More specifically, all scheduling decisions related to the continuous stages are modelled in the continuous timeframe, but the feasibility constraints are expressed using the discrete-time grid. The solution quality depends strongly on the duration of the time periods. A finer discretization results to more exact solutions, but to larger and more difficult to be solved models. Multiple tests have shown that a duration smaller than the fastest batch process is adequate since good schedules are generated in low computational times.

In order to further illustrate how time is represented in the developed models, let us consider the simple case illustrated in Figure 2.5. In this example three products *P1*,

P2 and *P3* are scheduled, over two continuous processing lines (*FS_1* and *FS_2*) and one packing line (*P_1*). The continuous timeframe determines, where each product is processed in the continuous processes ($Y_{s,j,p}$), in what sequence ($X^G_{j,p,p'}$, $X^I_{j,p,p'}$) and exact timing ($L_{s,p}$, $C_{s,p}$,). Simultaneously, the timing decisions are mapped on the discrete-time grid. At this point, it is assumed that a sterilization process takes place in all discrete-time points between the two continuous stages. This is denoted in the figure by the coloured blocks on top of the discrete grid, whose height expresses the number of sterilizers required for each product. This number is extracted by the following simple heuristic:

$$Number\ of\ sterilizers\ (\kappa_P) = \frac{Sterilization\ \ time\ of\ a\ batch}{Packing\ \ time\ of\ \ a\ batch}$$

, that allows for a constant production in the packing stage while using the minimum number of sterilizers. It must be noticed, that while a fully continuous process is modelled, this only occurs due to the employed aggregated approach. In reality, a mixed batch-continuous process takes place, and each product-lot is split into multiple batches in the batch stage. This process characteristic must be considered. In Figure *2.5* it is clear that the batch processing units are occupied between two time points, one being a little bit later than the start of the first continuous stage and the other a little bit earlier than the completion of the packing stage. This happens since the batch process will only start after processing the first batch in the continuous stage and will stop once the last batch enters the packing stage. A properly small period duration must be employed, to ensure a good quality of the results. At each time point, the total number of batch processing units used are monitored and bounded to not violate the maximum resource limit.

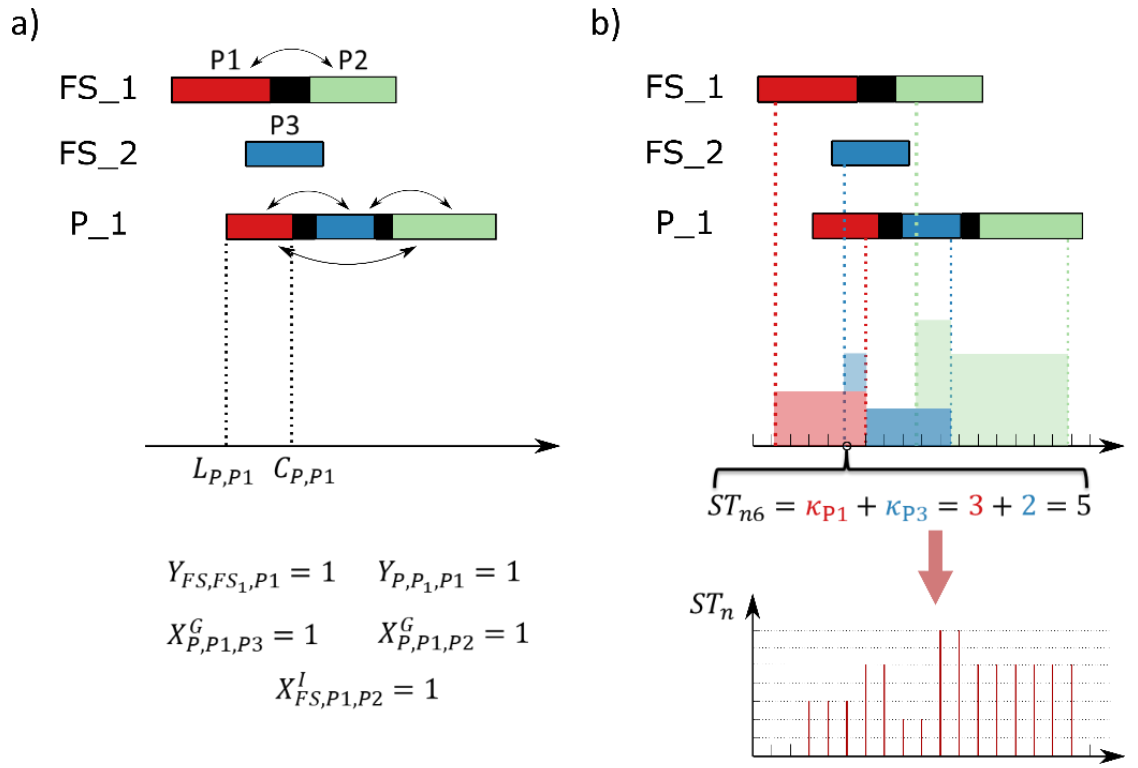

Figure 2.5: Time representation: a) continuous timeframe; b) discrete timeframe

2.3.2.2 General precedence model (M1)

All models based on the general precedence framework are significantly smaller compared to models generated using other continuous MILP frameworks. This is due to the fewer required constraints, making the general precedence model attractive for large-scale scheduling problems. For the problem under consideration, we propose an MILP model based on the aggregated approach presented in the previous subsection and the general precedence framework. Next, we present the developed model, categorizing the constraints according to the type of decisions they subject to.

Allocation constraints. Constraints (2.25) ensure that all products p, to be scheduled within the time horizon of interest, will be processed by a single unit j in every stage s, using the binary allocation variable $Y_{s,j,p}$. Constraints (2.26) activate the unit utilization variable V_j. In particular, they state that a unit is used ($V_j = 1$), whenever at least one product is processed by it ($Y_{s,j,p} = 1$).

$$\sum_{j \in (JP_j \cap JS_j)} Y_{s,j,p} = 1 \qquad \forall p \in I_p^{in}, s \in S \qquad (2.25)$$

$$V_j \geq Y_{s,j,p} \qquad \forall p \in I_p^{in} j \in (JP_{j,p} \cap JS_{j,s}), s \in S \qquad (2.26)$$

Timing constraints. Constraints (2.27) define the connection between the starting $L_{s,p}$ and the completion time $C_{s,p}$ of every product *p* at each stage *s*. Since all orders are completed in a single campaign the required processing time can be simple calculated by dividing the demand by the given processing rate $\tau_{j,p} = \frac{\zeta_p}{\tau_{j,p}^{rate}}$. Constraints (2.28) state that the completion time of a product *p* in each stage *s* must be larger than the necessary processing time of the product $\tau_{j,p}$ plus the processing times of all products *p'* that are previously processed in the same line ($X_{j,p,p'}^{G} = 1$). In the next constraints, the synchronization of production between stages is guaranteed. More specifically, constraints (2.29) ensure that the starting time of the packing process of a product, is larger than the starting time of the first process, plus the processing time of the first batch in the first stage $\tau_{j,p}^{FB}$ and the required sterilization time τ_p^{ster}. Similarly, constraints (2.30) guarantee the synchronization of the completion times in each stage.

$$C_{s,p} = L_{s,p} + \sum_{j \in (JP_{j,p} \cap JS_{j,s})} (\tau_{j,p} \cdot Y_{s,j,p}) \qquad \forall p \in I_p^{in}, s \in S \qquad (2.27)$$

$$C_{s,p} \geq \sum_{j \in (JP_j \cap JS_j)} (\tau_{j,p} \cdot Y_{s,j,p}) + \sum_{j \in (JP_j \cap JP'_j \cap JS_j)} \sum_{p' \in P_{p'}^{in}, p \neq p'} (X_{j,p',p}^{G} \cdot \tau_{j,p'}) \qquad \forall p \in I_p^{in}, s \in S \qquad (2.28)$$

$$L_{s,p} \geq L_{s-1,p} + \sum_{j \in (JP_{j,p} \cap JS_{j,s-1})} (\tau_{j,p}^{FB} \cdot Y_{s-1,j,p}) + \tau_p^{ster} \qquad \forall p \in I_p^{in}, s = 2 \qquad (2.29)$$

$$C_{s,p} \geq C_{s-1,p} + \sum_{j \in (JP_{j,p} \cap JS_{j,s})} (\tau_{j,p}^{LB} \cdot Y_{s,j,p}) + \tau_p^{ster} \qquad \forall p \in I_p^{in}, s = 2 \qquad (2.30)$$

Sequencing constraints. To ensure the proper sequencing of production, big-M constraints (2.31) and (2.32) are employed. The big-M parameter is set equal to the duration of the scheduling horizon. According to constraints (2.31), the starting time of a product *p'* processed after another product *p* in the same unit *j*, is forced to be larger than the starting time of product *p* plus the required processing time and the necessary changeovers $\gamma_{j,p,p'}$. Notice that these constraints are only defined for *p*<*p'*, therefore the complementary constraint set (2.32) must be introduced.

$$L_{s,p'} \geq L_{s,p} + \tau_{j,p} \cdot Y_{s,j,p} + \gamma_{j,p,p'} - M \cdot (1 - X^{G}_{j,p,p'}) - M \cdot (2 - Y_{s,j,p} - Y_{s,j,p'})$$

$$\forall\, p \in I^{in}_{p},\, p' \in P^{in}_{p'},\, s \in S,\, p < p',\; j \in (JPP_{j,p,p'} \cap JS_{j,s}) \qquad (2.31)$$

$$L_{s,p} \geq L_{s,p'} + \tau_{j,p'} \cdot Y_{s,j,p'} + \gamma_{j,p',p} - M \cdot (X^{G}_{j,p,p'}) - M \cdot (2 - Y_{s,j,p} - Y_{s,j,p'})$$

$$\forall\, p \in I^{in}_{p},\, p' \in I^{in}_{p'},\, s \in S,\, p < p',\; j \in (JPP_{j,p',p} \cap JS_{j,s}) \qquad (2.32)$$

Tightening constraints. Constraints (2.33) impose that a general precedence variable between two products is active, only when both products are processed in the same unit. On the other hand, constraint set (2.34) guarantees that in case both products p and p' are processed in the same unit j, then product p may be either processed before product p' or vice versa. In order to satisfy the given due dates τ^{ζ}_{p}, constraints (2.35) are introduced.

$$2 \cdot (X^{G}_{j,p,p'} + X^{G}_{j,p',p}) \leq Y_{s,j,p} + Y_{s,j,p'} \qquad \forall\, s \in S,\, p \in I^{in}_{p},\, p' \in I^{in}_{p'},\, p \neq p',\; j \in (JPP_{j,p',p} \cap JS_{j,s}) \qquad (2.33)$$

$$Y_{s,j,p} + Y_{s,j,p'} \leq V_{j} + X^{G}_{j,p,p'} + X^{G}_{j,p',p} \qquad \forall\, s \in S,\, p \in I^{in}_{p},\, p' \in I^{in}_{p'},\, p \neq p',\; j \in (JPP_{j,p,p'} \cap JS_{j,s}) \qquad (2.34)$$

$$C_{s,p} \leq \tau^{\zeta}_{p} \qquad \forall\, s \in S,\, p \in I^{in}_{p} \qquad (2.35)$$

Sterilization feasibility constraints. Constraints (2.36) - (2.39) utilize a discrete-time grid to enforce the sterilization stage-related feasibility constraints. The auxiliary binary variables $X^{ST}_{p,n}$ and $Z^{ST}_{p,n}$ are introduced to define the binary variable $CR^{ST}_{p,n}$ that is activated when a sterilization process occurs for a product p in time period n. In particular, constraints (2.36) enable variable $X^{ST}_{p,n}$ for all time periods after the completion of the first batch in the filling and sealing process, plus a waiting time W_p between the two processes. This variable is bounded to be less than Q_p hours, to ensure final product safety and quality. The exact time of each time period is calculated by the term $\delta \cdot n$, with

δ being the duration of each time period. Thus, constraints (2.36) define the beginning of a sterilization process for a product p. Similarly, constraints (2.37) set the completion of the sterilization process, by activating the corresponding variable $Z_{p,n}^{ST}$, for all time periods before the time point defined by the completion of the preparation process, plus the waiting time and the required sterilization time. It is assumed that the waiting time for both the first and last batch are equal, since defining two separate variables does not affect the quality of the solution, while the size of the model is further increased. Constraints (2.38) impose that a sterilization process for product p ($CR_{p,n}^{ST} = 1$) takes place for those time periods n, that both $X_{p,n}^{ST}$ (the process starts before n) and $Z_{p,n}^{ST}$ (the process finishes after n) are activated. Figure *2.6* illustrates graphically the role of each variable in the feasibility constraints.

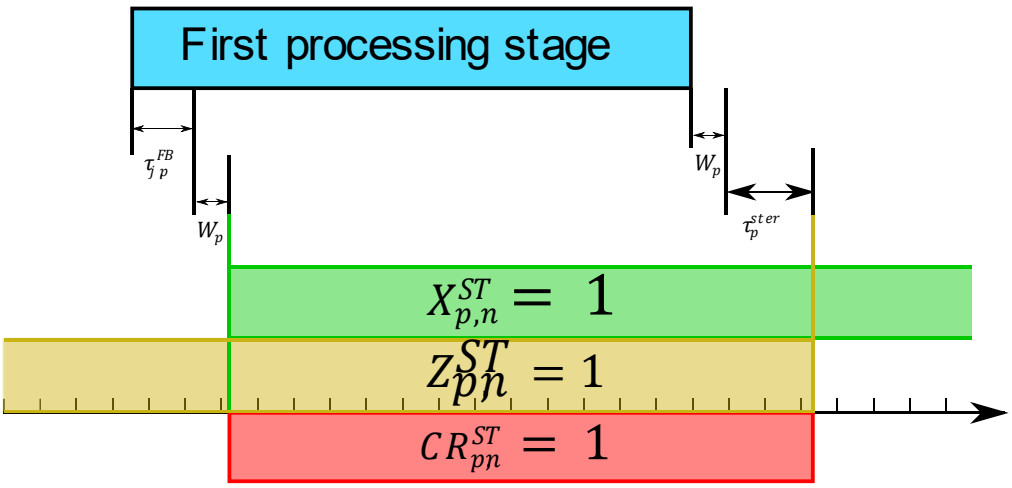

Figure 2.6: Explanation of binary variables introduced for the sterilization stage feasibility constraints

Finally, constraints (2.39) impose the resource capacity limitations for the sterilization stage. The number of sterilizers used for each product is defined by parameter κ_p, that is only enabled when a sterilization process occurs for this product. It is ensured that at each time point the total number of used sterilizers is less than the available resource v^{ST}.

$$X_{p,n}^{ST} \geq \frac{\delta \cdot n - L_{s,p} - W_p - \sum_{j \in JP_{j,p}} \tau_{j,p}^{FB} \cdot Y_{s,j,p}}{M} \qquad \forall p \in I_p^{in}, n \in N \qquad (2.36)$$

$$Z_{p,n}^{ST} \geq \frac{C_{s,p} + \tau_p^{ster} + W_p - \delta \cdot n}{M} \qquad \forall p \in I_p^{in}, n \in N \qquad (2.37)$$

$$CR_{p,n}^{ST} \geq X_{p,n}^{ST} + Z_{p,n}^{ST} - 1 \qquad \forall p \in I_p^{in}, n \in N \qquad (2.38)$$

$$\sum_{p \in P_p^{in}} (CR_{p,n}^{ST} \cdot \kappa_p) \leq v^{ST} \qquad \forall n \in N \qquad (2.39)$$

Extension - Labeller constraints. A significant resource limitation in many industrial facilities is the utilization of a single labeller machine in multiple packing units. Hence, these units cannot operate simultaneously. These design constraints must be considered to ensure the generation of feasible schedules. Therefore, we employ constraints (2.40) - (2.45), which were first proposed by Kopanos, Puigjaner, and Georgiadis (2011). The global sequencing variables $X_{j',p',j,p}^{L}$ are introduced for each pair of products *p'* and *p* that are assigned to different packing units sharing the same labeller. Constraints (2.40) and (2.41) impose that variables $X_{j',p',j,p}^{L}$ are activated when product *p'* starts in unit *j'* before product *p* starts being processed in another unit *j*. In constraints (2.42) a very small number λ is added to cope with the special case of two products starting at the same time. Auxiliary variables $Z_{j',p',j,p}^{L}$ are active whenever product *p'* is completed in unit *j'* after the starting time of product *p* in another unit *j*, as constraints (2.43) state. Finally, binary variables $CR_{j',p',j,p}^{L}$ are added, which denote that the production of *p'* in *j'* overlaps the one of *p* in unit *j*. As imposed by constraints (2.44), the variables are active only when both auxiliary variables are equal to one. Finally, constraints (2.45) do not allow any overlap in the production of products in lines sharing the same labeller machine.

$$L_{s,p'} - L_{s,p} \leq M \cdot (1 - X_{j',p',j,p}^{L}) + M \cdot (2 - Y_{s,j,p} - Y_{s,j',p'}) \qquad \begin{matrix} \forall p \in I_p^{in}, j \in JP_{j,p}, p < p' \\ j \in (JP_{j,p} \cap CL_{j,j'}), j' \in JP_{j',p'} \end{matrix} \qquad (2.40)$$

$$L_{s,p} - L_{s,p'} \leq M \cdot X_{j',p',j,p}^{L} + M \cdot (2 - Y_{s,j,p} - Y_{s,j',p'}) \qquad \begin{matrix} \forall p \in I_p^{in}, j \in JP_{j,p}, p < p' \\ j \in (JP_{j,p} \cap CL_{j,j'}), j' \in JP_{j',p'} \end{matrix} \qquad (2.41)$$

$$L_{s,p} - L_{s,p'} + \lambda \le M \cdot X^{L}_{j',p',j,p} + M \cdot (2 - Y_{s,j,p} - Y_{s,j',p'}) \qquad \begin{array}{l} \forall p \in I^{in}_{p}, j \in JP_{j,p}, p > p' \\ j \in (JP_{j,p} \cap CL_{j,j'}), j' \in JP_{j',p'} \end{array} \qquad (2.42)$$

$$C_{s,p'} - L_{s,p} \le M \cdot Z^{L}_{j',p',j,p} + M \cdot (2 - Y_{s,j,p} - Y_{s,j',p'}) \qquad \begin{array}{l} \forall p \in I^{in}_{p}, j \in JP_{j,p} \\ j \in (JP_{j,p} \cap CL_{j,j'}), j' \in JP_{j',p'} \end{array} \qquad (2.43)$$

$$CR^{L}_{j',p',j,p} \ge Z^{L}_{j',p',j,\mathrm{p}} + X^{L}_{j',p',j,p} - 1 \qquad \begin{array}{l} \forall p \in I^{in}_{p}, j \in JP_{j,p} \\ j \in (JP_{j,p} \cap CL_{j,j'}), j' \in JP_{j',p'} \end{array} \qquad (2.44)$$

$$\sum_{p' \in P^{in}_{p}, p' \ne p} \sum_{j' \in (JP_{j',p'} \cap CL_{j,j'})} CR^{L}_{j',p',j,p} \le 0 \qquad \forall p \in I^{in}_{p}, j \in JP_{j,p} \qquad (2.45)$$

Objective. Goal of this model is the minimization of the production makespan (2.46).

$$C^{max} \ge C_{s,p} \qquad \forall p \in P^{in}_{p}, s = 2 \qquad (2.46)$$

2.3.2.3 Unit-specific general precedence model (M2)

Despite their computational prowess, general precedence models cannot be used when changeover minimization is the main overarching goal of the scheduling problem. To consider this objective, a unit-specific general precedence model is developed. This model (M2) is very similar to the previously presented M1 model, sharing most constraints, with the main difference being the introduction of immediate precedence variables $X^{I}_{j,p,p'}$. More specifically, model M2 consists of constraints (2.25) – (2.27), (2.29) – (2.45) and the following:

$$\begin{aligned} C_{s,p} \ge & \sum_{j \in (JP_j \cap JS_j)} (\tau_{j,p} \cdot Y_{s,j,p}) \\ & + \sum_{j \in (JPP_{j,p,p'} \cap JS_j)} \sum_{p' \in P^{in}_{p'}, p \ne p'} (X^{I}_{j,p',p} \cdot \gamma_{j,p',p} + X^{G}_{j,p',p} \cdot \tau_{j,p'}) \end{aligned} \qquad \forall p \in P^{in}_{p}, s \in S \qquad (2.47)$$

$$L_{s,p'} \ge L_{s,p} + \tau_{j,p} \cdot Y_{s,j,p} + \gamma_{j,p,p'} \cdot X^{I}_{j,p,p'} - M \cdot (1 - X^{G}_{j,p,p'}) \qquad \begin{array}{l} \forall p \in P^{in}_{p}, p' \in P^{in}_{p'}, s \in S, \\ p \ne p', j \in (JPP_{j,p,p'} \cap JS_{j,s}) \end{array} \qquad (2.48)$$

$$\sum_{p \in (P^{in}_{p} \cap JP_{j,p})} \sum_{p' \in (P^{in}_{p} \cap JP_{j,p}), p' \ne p} X^{I}_{j,p,p'} + V_j = \sum_{p \in (P^{in}_{p} \cap JP_{j,p})} Y_{s,j,p} \qquad \forall j \in JS_{j,s}, s \in S \qquad (2.49)$$

$$\sum_{p' \in (P_{p'}^{in} \cap JP_{j,p'}), p' \neq p} X_{j,p,p'}^{I} \leq Y_{s,j,p} \qquad \forall p \in P_p^{in}, j \in JS_{j,s}, s \in S \qquad (2.50)$$

$$\sum_{p' \in (P_{p'}^{in} \cap JP_{j,p'}), p' \neq p} X_{j,p',p}^{I} \leq Y_{s,j,p} \qquad \forall p \in P_p^{in}, j \in JS_{j,s}, s \in S \qquad (2.51)$$

$$X_{j,p,p'}^{I} \leq X_{j,p,p'}^{G} \qquad \forall p \in P_p^{in}, p' \in P_{p'}^{in}, p \neq p' \quad j \in JPP_{j,p,p'} \qquad (2.52)$$

$$CH = \sum_{j \in JPP_{j,p,p'}} \sum_{p \in P_p^{in}} \sum_{p' \in P_{p'}^{in}, p \neq p'} (\gamma_{j,p,p'} \cdot X_{j,p,p'}^{I}) \qquad (2.53)$$

Constraints (2.47) constitute an alteration of constraints (2.28), since they guarantee that the completion time of a product *p* in stage *s* is larger than the required processing time, plus the processing time of all previously completed products in the same line, plus the changeover between product *p* and its direct predecessor *p'*. In contrast to model M1, a single set of sequencing constraints (2.48) is required, which forces the starting time of product *p'* to be larger than the starting of product *p* that is processed right before it, plus the processing time of *p* and the required changeover time. Four additional tightening constraints are employed. More specifically, constraints (2.49) state that the total number of processed products in a unit in each stage must be equal to the sum of enabled immediate precedence variables in that unit plus the unit activation variable. Constraints (2.50) and (2.51) impose that at most one product *p'* is processed right before or after *p*. Finally, constraints (2.52) guarantee that a product *p* can be an immediate predecessor of another product *p'* only if it is also a general predecessor. The objective of model M2 is the minimization of the total changeover time CH, as depicted by constraint (2.53).

2.3.2.4 Decomposition algorithm

The aggregated modelling approach presented in the previous subsection significantly reduces the combinatorial complexity of the problem. However, the direct solution of the MILP model in real-life industrial problems still requires large computational effort, thus resulting in intractable case studies. Moreover, the industry requires the fast solution of the weekly scheduling problem. This will allow production engineers to undergo multiple what-if analyses, and promptly encounter any order-

related uncertainties, like sudden change in demands, cancellations, or arrivals of new orders. The main goal of this study is to generate fast near-optimal schedules, which will be readily available to the decision-makers. This is essential for the developed strategy to be potentially used as the core of a future computer-aided scheduling tool that will be utilized by the production engineers. Therefore, to satisfy the prerequisites set by the industry a decomposition algorithm is employed, that further reduces the complexity of the optimization problem.

An order-based decomposition algorithm is employed to split the initial problem into smaller subproblems. The final schedule is generated iteratively. In each iteration, only a subset of the original set of product orders $p \in I_p^{in}$ is scheduled. Therefore, the generated MILP models are smaller and can be solved much faster. A characteristic of the developed approach, that strongly affects the quality of the solution, is the insertion policy, which consists of: a) the way products are sorted and b) the number of products optimally scheduled in each iteration. Regarding the first decision, multiple possible sorting algorithms were studied. The best solutions were extracted when sorting from largest to smallest product order size was chosen. This may not be trivial but can be easily justified since larger orders occupy more time in the scheduling horizon. So, in case other smaller orders are scheduled first, this may be done in a manner that does not allow for the optimal placement of the larger orders. The second decision is a user-defined parameter (σ). Larger values result in better solutions since the initial problem is less decomposed, but on the other hand, require more computational time. Thus, the value of this parameter must be set as high as possible, but not so large that the computational limitations of the examined study case are not met.

In Figure *2.7* a schematic representation of the developed solution strategy is presented. The input in this method is the plant data provided by the ERP system and Manufacturing Execution System (MES) and the insertion policy as defined by the user. In the pre-processing step the orders are sorted according to the preferred sorting algorithm and then the batching algorithm calculates all batch related parameters. Then, the scheduled problem is solved through an iterative method. The first σ products are inserted in the aggregated models presented in the previous subsection and the MILP model for the specified subproblem area is solved. The selected model depends on the scheduling problem's overarching goal. In particular, for makespan minimization, model

M1 is used, while model M2 is employed when changeover minimization is the main objective. Afterward, the unit allocation and the general precedence variables are fixed for the subproblem area. All other related variables, like the utilization of sterilizers and the completion and starting times for the products already scheduled can be freely adjusted in the next iterations to ensure flexibility and improve final results. Then, the algorithm returns to the initial step of the iterative method and the next set of products is inserted. When all product-orders are considered, the complete schedule is generated.

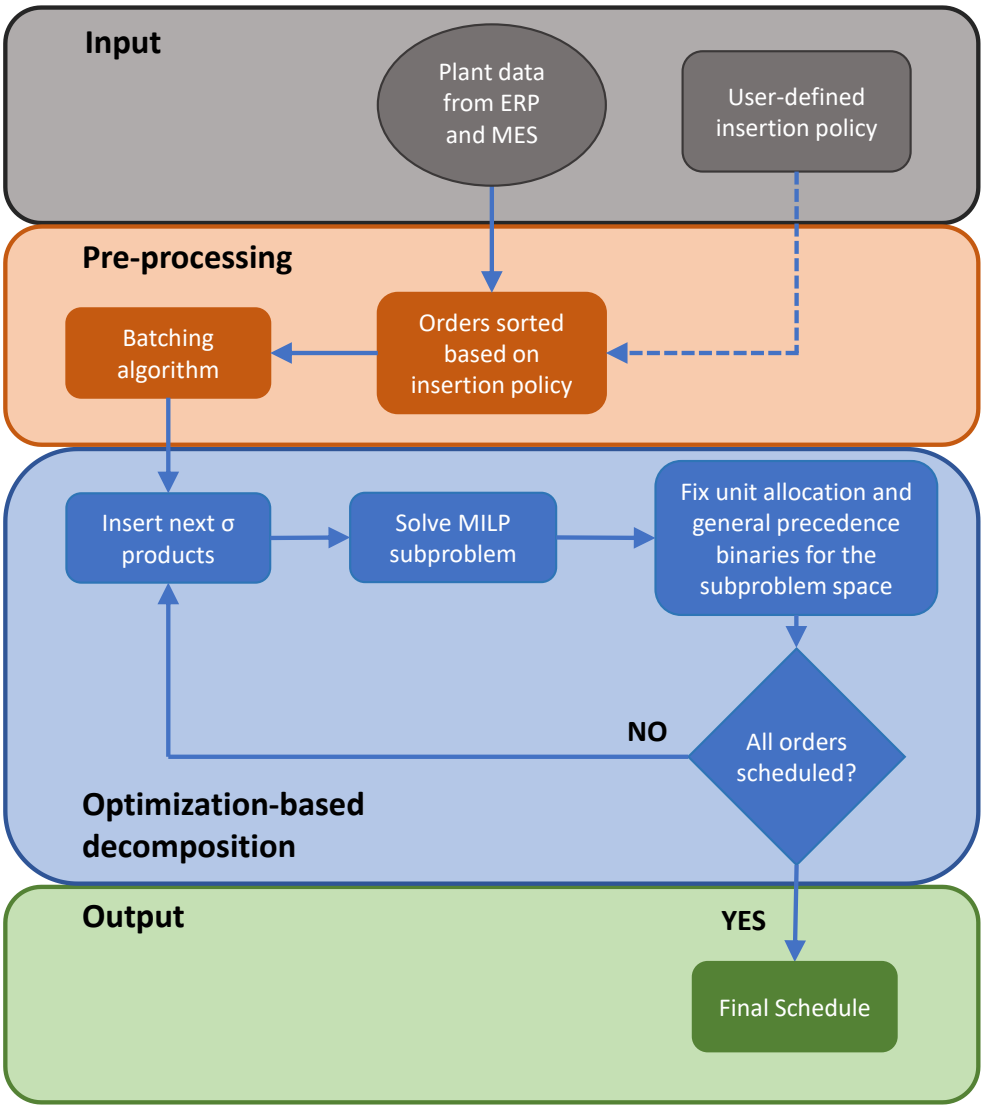

Figure 2.7: Optimization-based solution strategy

In Figure *2.8* an illustrative example displaying the allowed and forbidden sequencing decisions, when employing the decomposition algorithm, is presented. In this

simple example, we assume that only one unit exists. Two products have been already scheduled, while in the current iteration, just one product is newly inserted. It is illustrated, that the new product can be freely placed anywhere in the scheduling horizon and in any sequence to the others. However, the sequence between the already scheduled products is set and therefore cannot be changed. Notice, that the immediate precedence variables are not fixed when model M2 is used. Thus, the flexibility in changing decisions in future iterations of the iterative method is increased, which leads to schedules closer to optimality.

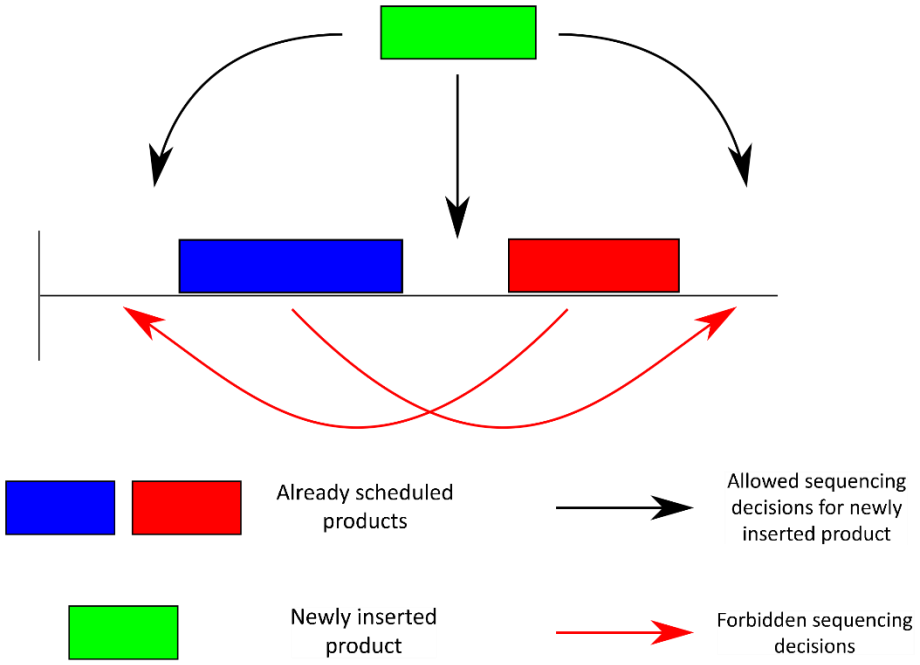

Figure 2.8: Flexibility of sequencing decisions

2.4 Computational analysis

In this section we display the efficiency of the proposed mathematical frameworks using a small illustrative example. We consider a multistage multiproduct facility, consisting of three processing stages. The first stage comprises of two continuous lines, next follows a sterilization stage consisting of two batch units and finally the products are packaged in two packing lines. A total of 25 products are produced during the 5-day scheduling horizon. Each product can be processed by any of the available sterilizers, but only by a subset of the continuous lines as shown in Table *2.1*, where {S1_L1; S1_L2} and {S3_L1;S3_L2} are the available processing lines of the first and second continuous stage

accordingly. The problem definition is slightly different for the two developed solution strategies. Approach A considers a daily demand with different orders for each product within the studied horizon. Moreover, it is assumed that the plant shuts down at the end of every day for maintenance purposes. On the contrary, Approach B is considered with a weekly demand with various due dates for each product order, while the plant operates 24/7. In addition to makespan minimization, approach B is employed also for the minimization of changeovers. Detailed data for the considered example are provided in Appendix A. All instances are solved using the GAMS interface and the CPLEX solved in a PC with a 1.8Ghz CPU and 8 GB of DDR4 RAM.

Table 2.1: Products that can be processed by the available continuous processing lines

	S1_L1	S1_L2	S3_L1	S3_L2		S1_L1	S1_L2	S3_L1	S3_L2
P1	1	1		1	**P14**	1		1	1
P2		1	1		**P15**	1	1	1	
P3		1	1	1	**P16**		1		1
P4	1	1	1		**P17**	1		1	
P5	1	1		1	**P18**	1		1	1
P6		1		1	**P19**	1	1	1	
P7	1		1		**P20**	1	1		1
P8	1	1		1	**P21**	1	1		1
P9	1	1		1	**P22**	1		1	1
P10		1		1	**P23**		1	1	
P11	1	1	1	1	**P24**	1		1	1
P12		1	1		**P25**	1		1	1
P13	1	1	1						

2.4.1 Approach A

Due to the small size of the examined example, only a temporal decomposition of the problem is employed. In each iteration of the algorithm, the daily schedule for all orders is optimized. An optimal solution that minimizes the production makespan in each individual day is extracted in just 1.7 CPU seconds. Table *2.2* shows the optimal objective value for each day, as well as the solution statistics for each daily MILP-subproblem. All orders are satisfied within the available horizon, while in some cases (day 2 and day 3) the optimal schedule is completed very fast, displaying the increased productivity potential of the studied facility. Notice that the solver spends most computational resources on the optimization of the first day, which happens to create the largest MILP-subproblem. It is shown that a low number of equations and variables is necessary for

the representation of this small, however complicated scheduling problem. As a result, optimal decisions can be taken instantaneously. Figure *2.9* Illustrates the Gantt chart of the optimal schedule for all processing stages. Each coloured block signifies a processing task of a batch/lot in the corresponding continuous line or sterilizer.

Table 2.2: Solution and model statistics using approach A on the illustrative example

Day	Objective value (hr)	Equations	Continuous Variables	Binary Vars	CPU (s)
1	22.29	615	128	248	1.55
2	19.71	226	80	92	0.05
3	13.18	163	48	72	0.03
4	23.69	220	56	93	0.02
5	20.26	121	80	52	0.02

2.4.2 Approach B

First, we consider the minimization of the production makespan employing model M1 in the context of the solution strategy developed in approach B. The size of the problem allows for a monolithic approach without the use of the proposed order-based decomposition strategy. Model M1 generates an optimal schedule with a minimal makespan of 71 hours in just 18.8 CPU seconds. The solution strategy achieves an improved synchronization between the processing stages and optimally exploits the available resources leading to a schedule which denotes that the plant's productivity can be significantly increased. The resulting model consists of 7563 equations, 8032 binary variables and 126 continuous variables. Notice the high number of binary variables, which originate from the utilization of a discrete time horizon required for the introduced feasibility constraints. However, the model is tight enough and can provide optimal solutions in low computational times. Figure *2.10* presents the optimal Gantt chart of the continuous stages for makespan minimization. Due to the employed aggregated approach, detailed optimal decisions are not generated for the sterilization stage. However, the available sterilizes can realize the proposed optimal schedule without affecting the solution quality.

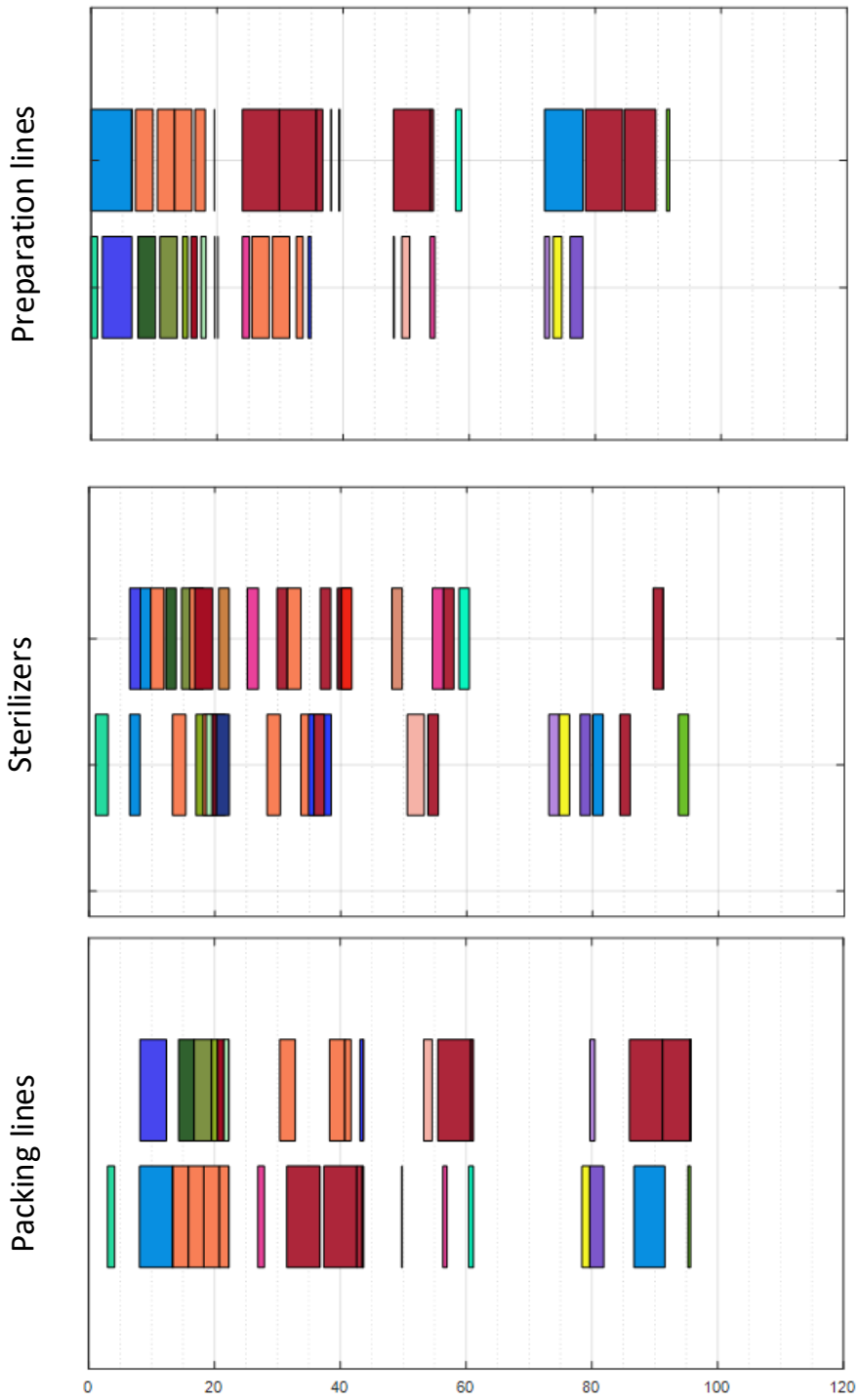

Figure 2.9: Gantt chart for makespan minimization extracted using approach A

Furthermore, we examine the impact of the decomposition strategy on the extracted schedules. Therefore, three decomposition scenarios are tested. In particular, the mathematical framework of approach B is employed using i) a 1-by-1, ii) a 5-by-5 and iii) a 10-by-10 insertion policy. The comparative results are shown in Table 2.3. As expected, the holistic approach provides the best possible solution, while a finer

decomposition (schedule optimized for fewer products in each iteration) leads to faster but worse solutions. An interesting conclusion is drawn by the fact that the solution extracted by a less fine decomposition (10-by-10) is only 5% worse than the one provided by the monolithic approach, when it requires only a tenth of the CPU time, thus displaying the effectiveness of the proposed mathematical framework. This is even more evident in larger problem instances and is further discussed in subchapter 3.2.

Table 2.3: Comparing the solution for various decomposition approaches

Insertion policy	**Objective (hr)**	**CPU (s)**	**Improvement (%)**
1 by 1	88	0.5	-23.94
5 by 5	80	1.5	-12.68
10 by 10	75	1.8	-5.64
Monolithic	71	18.8	0

Next, the same problem is examined but with the overarching goal being the minimization of changeovers. Therefore, model M2 is used. Compared to the minimization of makespan, minimizing the total changeover time is a more challenging task. Monolithically solving the model without the incorporation of a decomposition algorithm, cannot provide an optimal solution within a reasonable computational time (900 s) for the problem at hand. The best schedule is generated when utilizing a 10-by-10 insertion policy in the proposed decomposition algorithm. The solution strategy achieves a minimal changeover time of 10.4 hours and generates the optimal schedule illustrated in Figure *2.11* in just 16 seconds.

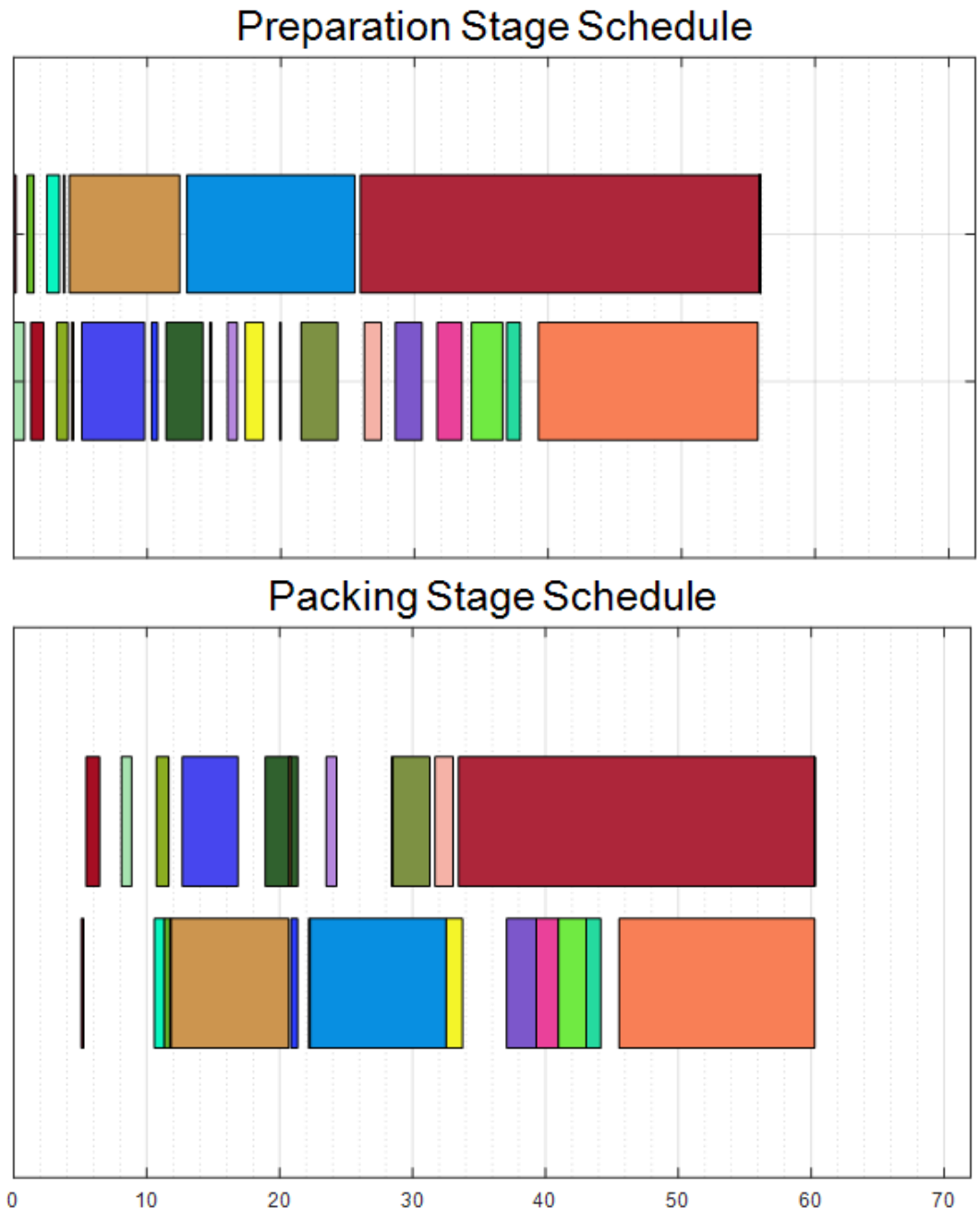

Figure 2.10: Gantt chart for makespan minimization extracted using approach B

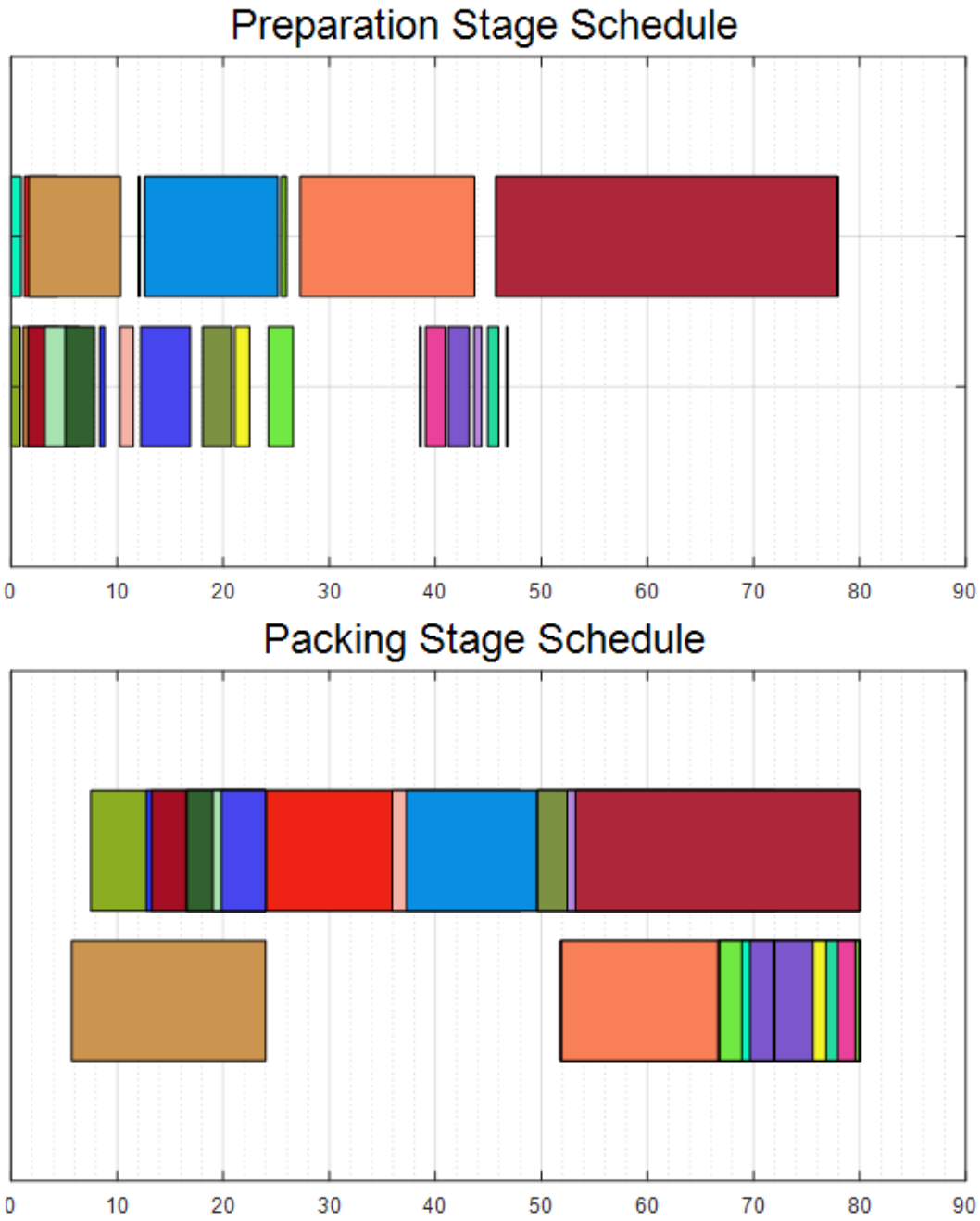

Figure 2.11: Gantt chart for changeover minimization extracted using Approach B

2.5 Conclusions

This chapter considers the optimization-based scheduling of multistage multiproduct facilities with mixed batch and continuous processes. The problem under consideration illustrates significant complexity, due to the mixed type of processing stages, and the numerous shared resources. The inherent complexity of this type of problems requires the development of novel solution strategies. Two new mathematical frameworks were proposed, both consisting of three main pillars: i) a common pre-processing step for the batching subproblem, ii) an MILP model and iii) a decomposition algorithm. Core of the first approach is a new precedence-based model that cleverly reduces the size of the generated models by utilizing a cyclic allocation heuristic in the sterilization stage. In the second approach a novel set of feasibility constraints is introduced in two precedence-based models, one for makespan and one for changeover minimization. Both approaches display distinct strengths. In approach A, detailed optimal schedules for each processing stage are generated. Approach B considers the sterilization stage in an aggregated way, thus ignoring detailed scheduling decisions. This approach is computationally more efficient and can also consider the changeover minimization objective. As shown in the computational analysis, both methods can efficiently deal with the scheduling problem under consideration and can be used according to the specific goals of the optimization, the plant design and the operational characteristics. The considered make-and-pack structure (one or multiple batch or continuous processes followed by a packing stage) is typically met in most food and consumer packed good industries, but also in other type of industries like pharmaceuticals and specialty chemicals, hence the developed mathematical framework can assist the decisions makers in a great variety of process industries real-life scheduling problems.

Nomenclature

Indices

$p, p' \in P$	products to be processed within the scheduling horizon
$b, b' \in B$	batches of products required to fulfil the order
$j, j' \in J$	processing units
$s \in S$	processing stages
$n \in N$	time periods of considered horizon

Sets

	Common for both approaches
I_p^{in}	subset of products being optimized in an iteration of the decomposition algorithm
$JP_{j,p}$	Mapping set defining the units *j* that can process product *p*
$JS_{j,s}$	mapping set defining lines *j* that belong in stage *s*
$JPP_{j,p,p'}$	mapping set defining units *j* that can process both products p and *p'*
	Approach A
I_n^{in}	days considered in the decomposition algorithm
$PB_{p,b,n}$	denotes the batches *b* of product *p* processed in period *n*
$SB_{p,n}$	orders of product *p* in period *n* that comprise of a single batch
$Cyc_{p,b,n}$	batches b of product *p* in period *n* that are first in the cyclic heuristic

$PBL_{p,b,n}$	last batch of product *p* in period *n*
$FCB_{p,b,n}$	subset denoting the first $\kappa_{p,n}$ batches of product *p* in time period *n*
$LCB_{p,b,n}$	subset denoting the last $\kappa_{p,n}$ batches of product *p* in time period *n*
ST_s	subset of *s* denoting the sterilization stage
CS_s	subset of *s* denoting the continuous stages
FST_j	first sterilizer
LST_j	last sterilizer

Approach B

$CL_{j,j'}$	packing lines *j* and *j'* utilizing the same labeller device

Parameters

Common for both approaches

$\tau_{j,p}^{rate}$	processing rate of each product *p* processed by continuous line *j*
$\gamma_{j,p,p'}$	changeover time required between product *p* and *p'* processed in line *j*
τ_p^{ster}	sterilization time required for each product *p*
χ_p	capacity of cart when filled with product *p*
χ^{ST}	number of carts to fill each sterilizer
Q_p	Maximum allowed waiting time between the preparation and the sterilization stage
M	big-M number

Approach A

$\tau_{j,p,n}$	processing time of each product *p* processed by continuous line *j*

$\tau^{FB}_{j,p,n}$	processing time for the first batch of each product *p* processed by continuous line *j* in period *n*
$\tau^{LB}_{j,p,n}$	processing time for the last batch of each product *p* processed by continuous line *j* in period *n*
$\kappa_{p,n}$	number of sterilizers for each product order *p* used according to the applied cyclic heuristic in period *n*
$\zeta_{p,n}$	demand for product *p* in period *n*
$n^{c}_{p,n}$	number of carts used for product *p* in period *n*
$n^{b}_{p,n}$	number of batches used for product *p* in period *n*
$n^{FB}_{p,n}$	number of full batches used for product *p* in period *n*
$q^{FB}_{p,n}$	quantity of product *p* processed in a full batch in period *n*
$q^{LB}_{p,n}$	quantity of product *p* processed in the last batch in period *n*

Approach B

$\tau_{j,p}$	processing time of each product *p* processed by continuous line *j*
$\tau^{FB}_{j,p}$	processing time for the first batch of each product *p* processed by continuous line *j*
$\tau^{LB}_{j,p}$	processing time for the last batch of each product *p* processed by continuous line *j*
κ_{p}	number of sterilizers for each product order *p* used according to the applied cyclic heuristic
τ^{ζ}_{p}	due date for product *p*
ζ_{p}	demand for product *p*
n^{c}_{p}	number of carts used for product *p*
n^{b}_{p}	number of batches used for product *p*
n^{FB}_{p}	number of full batches used for product *p*
q^{FB}_{p}	quantity of product *p* processed in a full batch
q^{LB}_{p}	quantity of product *p* processed in the last batch
v^{ST}	number of available sterilizers

λ	a very small number

Variables

Binary

	Approach A
$Y_{p,s,j,n}$	= 1 when product *p* is processed in unit *j* in processing stage *s* and period *n*
$\overline{Y}_{p,b,j,n}$	= 1 when a batch b of product *p* is processed in sterilizer *j* in period *n*
$Y^F_{p,j,n}$	= 1 when the first batch of product *p* is processed in sterilizer *j*
$X_{p,p',s}$	= 1 when product *p* is processed before product *p'* in stage *s*
	Approach B
$Y_{s,j,p}$	= 1 when product *p* is processed in unit *j* in processing stage *s*
V_j	= 1 when unit *j* is being utilized
$X^G_{j,p,p'}$	= 1 when product *p* is processed before product *p'* in unit *j*
$X^I_{j,p,p'}$	= 1 when product *p* is processed right before product *p'* in unit *j*
$X^L_{j',p',j,p}$	= 1 when product *p'* starts being processed in unit *j'* before or exactly *p* at the time that product *p* starts in unit *j*
$Z^L_{j',p',j,p}$	=1 when product *p'* is completed being processed in unit *j'* after the starting time of product *p* in unit *j*
$CR^L_{j',p',j,p}$	= 1 when the production of *p'* in *j'* overlaps the one of *p* in another unit *j*
$X^{ST}_{p,n}$	auxiliary variable for $CR^{ST}_{p,n}$
$Z^{ST}_{p,n}$	auxiliary variable for $CR^{ST}_{p,n}$

$CR^{ST}_{p,n}$	= 1 when sterilization process for product *p* takes place for those time periods *n*,

Continuous

	Approach A
$C_{p,b,s,n}$	completion time for batch *b* of product *p* in processing stage *s* and period *n*
$L_{p,b,s,n}$	starting time for batch *b* of product *p* in processing stage *s* and period *n*
$W_{p,b,s,n}$	waiting time of processing batch *b* for product *p* between stages in period *n*
	Approach B
$C_{s,p}$	completion time for product *p* in processing stage *s*
$L_{s,p}$	starting time for product *p* in processing stage *s*
W_p	waiting time between stages

Objectives

CH	total changeover time
C_{max}	makespan

Chapter 3

Real-life Industrial Applications

3.1 Introduction

The importance of applying optimization-based scheduling solutions on real-life industrial cases is widely recognized. However, only a few successful industrial applications are reported, e.g. in the Dow Chemical Company (Wassick and Ferrio 2011), despite key research developments in the field of production scheduling (Georgiadis et al., 2019a). The main reason for this disconnect between academia and industry is the fact that most contributions address small- or at best medium-sized problem instances, that do not represent the size and complexity of real-life industrial facilities. Hence, there is a continuously growing interest in solving large scheduling problems. It must be however emphasized, that the successful use of computer-aided scheduling tools by the industrial operators and managers, is not solely dependent on the efficiency of the proposed solution strategies. Numerous practical issues need to be resolved prior to the on-site application, like ease of use, development and maintenance of the application, stable system integration, and ability to dynamically make minor adjustments and adapt to new information.

Food industrial facilities display characteristics like intermediate due dates, multiple mixed batch and continuous production stages and product quality/safety-related considerations, that substantially complicate the optimization of the scheduling decisions. The above considerations combined with market trends that impose the gradual expansion of the product portfolio, product demand profiles which are characterized by high variability and low volumes and many identical production units and shared resources, make the application of optimization-based scheduling solutions in real-life industrial problems extremely challenging.

In this chapter we address the real-life optimal scheduling problem of a large multistage multiproduct facility that comprises of both continuous and batch processes.

Researchers have considered a plethora of industrial case studies from various subsectors of the food industry in the last decades. However, most studies focus on small to medium-sized problems (Doganis and Sarimveis (2007), Simpson and Abakarov (2009), and Liu et al., (2010)) or simple production processes (Kopanos et al., (2010a), Sel et al., (2017) and Georgiadis et al., (2019b)). The process under consideration is characterized by many involved items in terms of processing stages, available units and products to be scheduled. Moreover, tight operating and design constraints, as well as the need to generate near-optimal schedules in low CPU times, lead to a scheduling problem of extreme combinatorial complexity, that has never been systemically examined and efficiently solved in the open literature. Therefore, we employ the frameworks proposed in chapter 2 to successfully address a real-life large-scale industrial scheduling problem.

3.2 Industrial Problem

A real-world food process industry is considered in this chapter. More specifically, the scheduling problem of the Spanish industry Frinsa del Noroeste S.A., one of the largest canned fish producers in Europe, is addressed. The studied facility can produce more than 400 product codes, a number that is constantly increasing, to cover market needs and fulfils more than 100 orders every week. The production process is extremely complicated, comprising of several, batch, and continuous processes. In order to simplify the description of the production process, we identify four major processing stages, in particular, thawing, filling and sealing, sterilizing and packing, each consisting of multiple parallel units (Figure 3.1). Initially, the fish arrives in tracks in the form of frozen blocks, which are defrosted in the thawing stage. Then, the blocks are cut in the proper size and filled in cans along with other ingredients (e.g., tomato-sauce, oil, brine etc.) according to the product's recipe. In the same processing stage, the cans are sealed and transferred into carts. Afterward, the carts are manually inserted in the sterilization retorts. Each sterilizer has a capacity of nine carts. To avoid the growth of bacteria, the transfer between the filling and sealing lines and the sterilization retorts must guarantee a near zero-wait policy. Therefore, no more than two hours must elapse between the completion of the filling and sealing process and the initiation of the sterilization process. The sterilization process is critical for food safety and final product quality. The cans are heated at a temperature of around 110°C, which is maintained for a specific time,

ensuring the targeted bacteria lethality, and finally, they are cooled down to room temperature. Depending mainly on the size and shape of the cans, but also on the type of fish and the rest of the ingredients, the duration of the sterilization process varies from 82 to 180 minutes. Horizontal retorts are used, while the temperature is managed through a water spraying system. After the completion of the sterilization process, the carts are manually extracted from the retorts and are transferred to the packing stage, where the cans are packaged in the final product form (single, 6-pack, boxes etc.). An important operation of this stage is labelling. However, not all packing lines have an individual labeller. In particular, lines 1-2 and 5-6, share the same labelling machine, therefore they cannot operate simultaneously. Finally, after the completion of the packing stage, the end products are stored in the warehouse, to be distributed in the market.

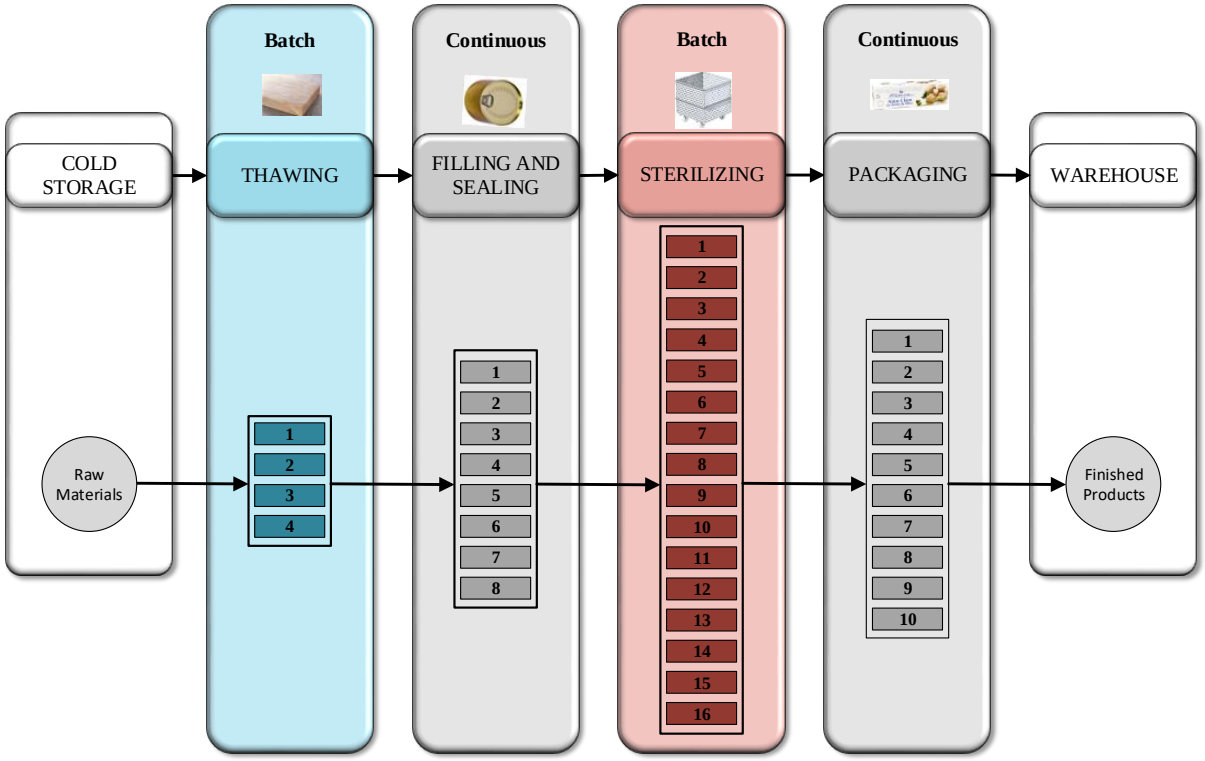

Figure 3.1: Process description

The plant can be described as a multistage, multiproduct facility that combines both batch (thawing, sterilizing) and continuous (filling and sealing, packing) processes with multiple parallel units. In particular, four thawing chambers, eight filling and sealing lines, 16 sterilizers and ten packing lines exist, making up a total of 38 available units in the whole production process. Moreover, more than 100 different products are to be

scheduled in a weekly basis. Consequently, an extremely large number of involved items is reported, making the scheduling problem under study extremely complex. One should also consider that the order-sizes are usually larger than the sterilization chamber's capacity, therefore each order is split into multiple order-batches, thus significantly increasing the total number of items to be scheduled. An important feature of the plant is the high production flexibility. Each product can be processed by all batch units, but only specific continuous lines, which have different processing rates. Furthermore, the processing time of each stage significantly varies, thus making the efficient synchronization of all processes a difficult task. In order to reduce the problem's size, it was concluded that the thawing stage can be omitted for two main reasons: a) the capacity of the thawing chambers is significantly larger than the rest of the processing lines, b) the defrosted fish can be stored in the chambers for a significant amount of time (more than 24hours). Therefore, any schedule generated by considering all other stages, can be fulfilled by the thawing stage. Despite this simplification, the complex mixed batch and continuous process, combined with the number of production units and orders, production flexibility and the absence of clear bottlenecks, results to a computationally exhaustive scheduling problem.

The plant operates from Monday to Friday, however in cases of large weekly demands overtime operation during the weekend is allowed. Therefore, the short-term scheduling horizon varies from 5 to 7 days depending on the case study, whereas all processing units are available 24 hours each day. Most products have a single due date at the end of the scheduling horizon; nonetheless, some exceptions may occur. Full demand satisfaction is a prerequisite and orders must be delivered on time, so tardiness is not allowed. Due to product quality considerations and space-related limitations, once a product campaign starts in the thawing stage, it must be carried out until the completion of all processing stages. Moreover, a single campaign policy is favored in the plant, therefore order splitting is not possible.

In practice, production schedules are generated manually by the plant engineers. The extreme combinatorial complexity of the underlying problem makes it impossible for the production engineers to consider the weekly integrated scheduling problem of all processing stages even using simple heuristic rules. In an attempt to generate a feasible schedule, they decompose the decision-making process into multiple steps. First, they

receive the weekly demand from the ERP system and plan the daily production based on capacity limitations. They consider the filling and sealing stage as the most critical process, due to the existence of large changeover times. Therefore, a weekly plan for the filling and sealing stage is firstly generated, so that large changeover times are avoided. Afterward, this plan is thrown over the wall to the department responsible for the packing stage, which checks the feasibility of the plan. At this point, there is a constant back and forth communication until a final plan is achieved. After settling on a weekly plan, a daily schedule is generated, two days before the day under examination, separately for the filling and sealing and the packing stage. During the whole procedure, the sterilizers are not considered at all. The basic rationale of the production engineers is that the main reason for reduced productivity is the existence of changeover times, therefore they try to minimize them separately in each stage. This approach is however myopic since they do not consider at all the synchronization of production between stages and the limitations imposed by the sterilization stage. Consequently, the actual schedules vary significantly from the planned ones, thus requiring multiple re-iterations throughout the week.

The complexity of the problem results in a decision-making approach which lacks efficiency and generates schedules far away from the optimal operation. The optimization-based frameworks proposed in Chapter 2 consider all involved stages and constraints which affect the efficiency of the generated schedules. Therefore, they are applied in this industrial case to assess their efficiency into dealing with real-life scheduling problems.

All data considered are real and provided directly by the plant's computer systems, so they correspond to the industrial reality faced by the schedulers. The demand is provided directly by the plant's ERP system, while all operational data, e.g., processing rates, changeover times etc., are supplied by the MES installed at the facility. Moreover, MES provides the Overall Equipment Effectiveness (OEE) factor of all processing lines, which represents any deviations from the lines' nominal speeds, due to i) equipment breakdowns, ii) minor stoppages, iii) reduced machine speeds, iv) start-up scrap and v) product scrap and is calculated based on historical data. Incorporating the OEE factors in the scheduling problem, provides a way to consider uncertainties on the processing rates, thus increasing the robustness of the generated schedules. All data are assumed to be

deterministic, while resources like manpower, steam, electricity etc. are not considered. All MILP models were implemented in GAMS 25.1 and solved in an Intel Core i7 @3.4Gz with 16GB RAM, using CPLEX 12.0.

3.2.1 Industrial application of approach A

We first consider the utilization of the detailed optimal production scheduling process. An industrial study case using real data from the Frinsa production plant is presented. In total 136 final products are to be scheduled, corresponding to a real weekly demand from a period with intensive production. Since the developed model cannot incorporate shared resource constraints, the related labelling constraints are not considered. To solve this complex case, the proposed solution strategy is utilized. In each iteration the daily schedule for half of the product-orders was chosen to be optimized. Goal of the optimization is the minimization of the daily production makespan. Optimality is reached for all iterations of the suggested solution strategy. Figure *3.2* illustrates the complete schedule generated for all units of every processing stage.

Compared to the real weekly schedule proposed by Frinsa, the optimized schedule of the proposed strategy illustrates interesting results. To satisfy the given demand, the manually derived schedule by Frinsa, requires the addition of a shift on Saturday, while the optimized schedule satisfies all orders within five days. The developed mathematical framework requires approximately one hour of CPU time for the solution of the problem which is acceptable for offline scheduling. However, it was in the desires of the production engineers to significantly reduce the total computational time, in order to allow for fast and efficient rescheduling actions, in case of possible disturbances within the considered horizon. So, despite the successful application of approach A in a real-life problem, it was incapable of proposing near-optimal schedules in computational times acceptable by the industry. Therefore, a more computationally efficient mathematical framework is necessitated to properly address the problem under consideration.

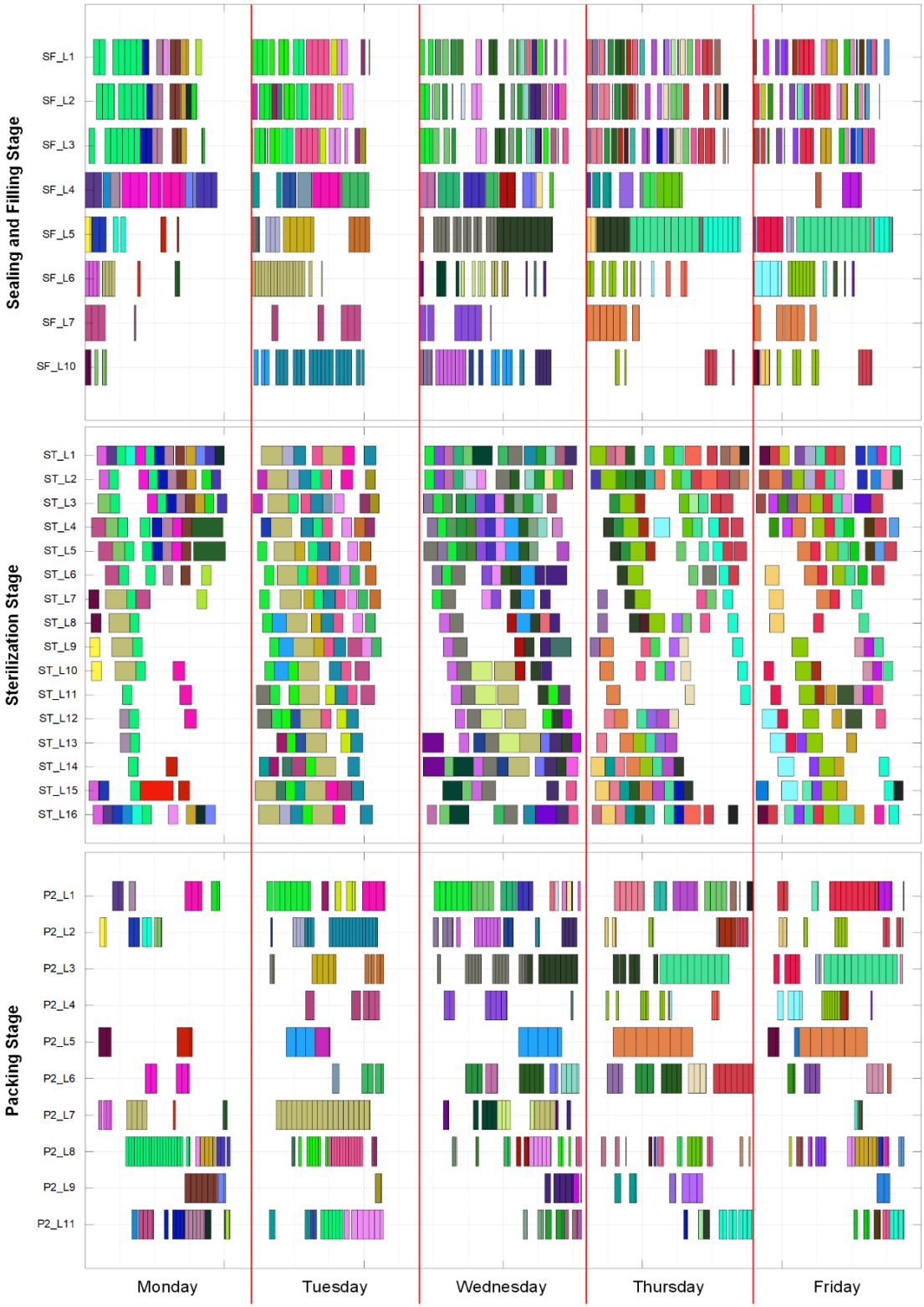

Figure 3.2: Gantt chart for makespan minimization using approach A for a real-life industrial problem

3.2.2 Industrial application of approach B

The applicability and efficiency of the MILP-based optimization framework presented in subchapter 2.3.2 is illustrated using real-life, large-scale industrial case studies, provided by the canned-fish facility.

Relevant labeller constraints are introduced in the packing stage. In particular, the pairs of packing lines *{P_1; P_2}* and *{P_5; P_6}* share the same labelling machine, therefore it is forbidden to operate simultaneously. The implementation of a discrete-time grid requires the discretization of the relevant scheduling horizon into equisized periods. A duration of one hour is chosen for each time period, since the longest sterilization process lasts 82 minutes. Employing a finer discretization may provide more exact solutions, but the computational cost is prohibitive for the solution of the problem in reasonable CPU times. A challenging prerequisite set by the production engineers is the total computational time required for the generation of near-optimal schedules, to be less than 15 minutes. This may be considered as a relatively small CPU time for weekly scheduling, however, such a low solution generation time will allow production engineers to run multiple what-if analyses and re-run the model whenever new information arrives in the plant. Thus, making a future computer-aided tool much more appealing to the production engineers and plant managers.

3.2.2.1 Problem size reduction

Let us first underline the impact the developed aggregated approach has on the industrial problem's size. The multistage, multiproduct, semi-continuous plant under consideration consists of four processing stages, i.e., thawing, filling and sealing, sterilization and packing. However, the utilization of the proposed aggregation approach reduces the optimization problem into two continuous processes (filling and sealing, packing). Exact schedules are generated only for these stages. However, due to the valid assumptions and the imposed feasibility constraints of the aggregated approach, the proposed schedules will be realized by all stages, without violating any capacity or other limitations. The total number of available sterilizers in the plant is 16 and they are modelled as a common renewable resource. The reduction of the problem's complexity using this approach is illustrated in Figure *3.3*, where all possible production routes for a single product are depicted. It is evident that the suggested aggregated approach

decreases substantially the underlying decisions and results into smaller and more efficient MILP models.

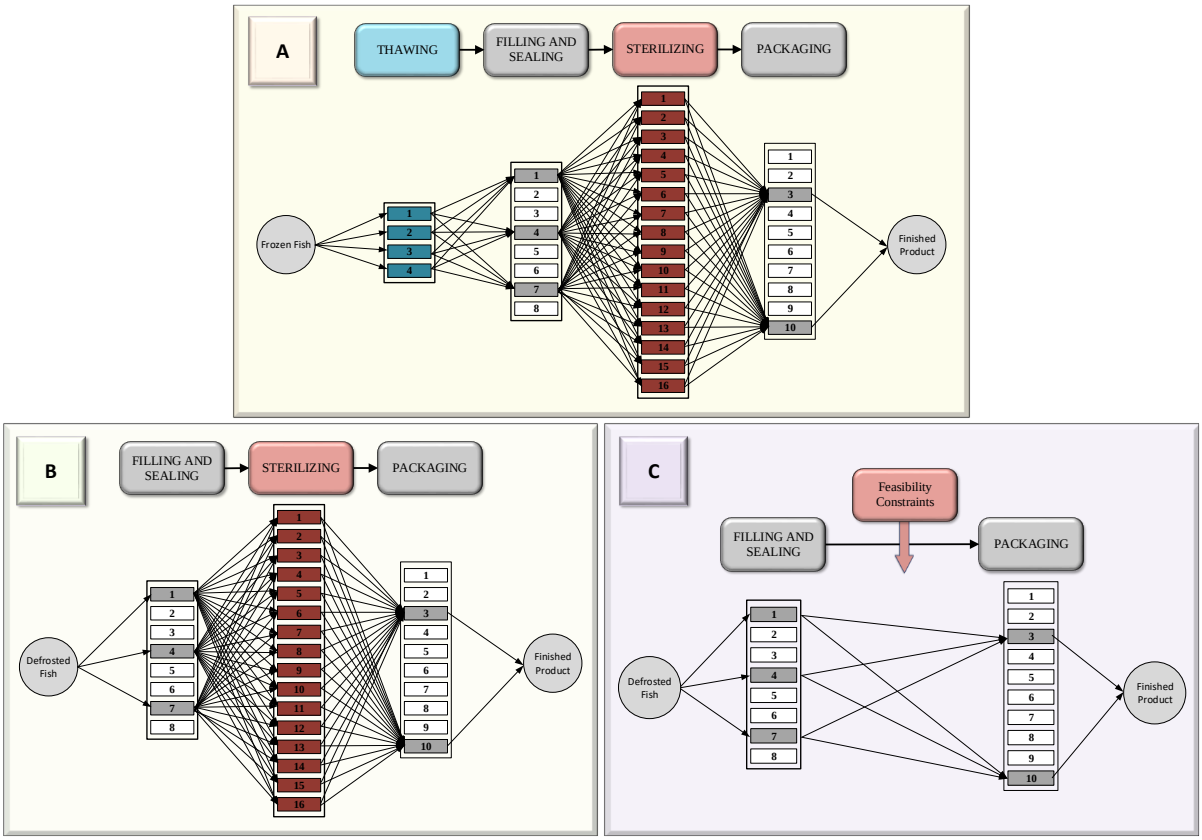

Figure 3.3: Possible production routes of a single product when a) considering the fully sized problem, b) omitting the thawing stage and c) explicitly modelling only the continuous stages.

3.2.2.2 Evaluation of the Decomposition Algorithm

The decomposition algorithm constitutes a crucial component of the proposed scheduling framework, as it allows the solution of this complex real-life problem in a computational time acceptable by the production engineers and managers of the specific industry. However, the fast generation of schedules is not the sole purpose of the proposed method. The quality of solution is essential, and it is the main reason for employing an optimization-based approach. It is clear, that the quality of the generated schedules is affected by the decomposition algorithm, as initially was shown in subchapter 2.4.2. Hence, it is important to evaluate the performance of the algorithm, by comparing the extracted solution with the truly optimal one. Therefore, three medium-sized problem instances (I - III) are considered, which correspond to daily demands of the Frinsa plant. The examined cases display an increasing complexity. In particular, 22,

31 and 35 products are to be scheduled in cases I, II and III, accordingly. All cases are solved twice, once for makespan (MK) and once for changeover (CH) minimization, resulting in a total of six instances. Each instance is solved once, directly applying the MILP model and then using four different decomposition steps, ranging from 1-1 to 10-10, while a time limit of 900s is imposed. In all instances a 10-10 decomposition was able to generate near-optimal solutions (<1.5%) in just a small fraction of the time required by the monolithic approach. Employing a finer decomposition leads to a faster generation of schedules, but also to worse solutions. Especially, a 1-1 or 2-2 decomposition may lead to non-integer solutions (I.CH, II.CH, I.MK) or solutions far from the optimal (I.CH). Case III.CH illustrates special interest since it is the most demanding problem instance (most products, difficult objective). Here it is evident, that for complex scheduling problems, the monolithic approach cannot return an optimal solution within the given CPU limit. However, the proposed decomposition strategy returns a better solution, even when applying a 1-1 decomposition step, which is close to the theoretical optimal one. In conclusion, these results illustrate that the proposed decomposition strategy does not only generate fast, but also high-quality solutions. A summary of the comparative study is presented in Table 3.1. The computational time and the objective value for all cases are given. Moreover, the integrality gap to the theoretically optimal solution is given for the cases solved using the monolithic approach. For the cases employing the decomposition approach, the gap displays the quality difference of the solution extracted to the one provided by the monolithic approach. A negative value means that the solution provided by the decomposition algorithm is better than the solution extracted by the monolithic approach.

3.2.2.3 Industrial case I

In this case, we study the scheduling problem of Frinsa del Noroeste over a time horizon of 5 days. The orders for 100 products are directly provided by the ERP system and correspond to the real demand profile scheduled by the production engineers in the plant. All demand-related data are deterministic, however, the use of OEE rates increases the robustness of the proposed schedules. Product demands along with all relevant operational data are provided in Appendix B. Due to confidentiality issues, the OEE rates are not explicitly given, but they are incorporated in the processing rates. The problem is

Table 3.1: Evaluation of the decomposition algorithm

Case	Monolithic			1-1			2-2			5-5			10-10		
	CPU (s)	Obj (hr)	Gap (%)	CPU (s)	Obj (hr)	Gap (%)	CPU (s)	Obj (hr)	Gap (%)	CPU (s)	Obj (hr)	Gap (%)	CPU (s)	Obj (hr)	Gap (%)
I.CH	118	8.17	0.00	-	-	-	13	11.00	34.64	29	8.95	9.54	59	8.17	0.00
II.CH	900	22.92	4.00	-	-	-	16	23.90	4.28	35	23.08	0.70	70	23.00	0.35
III.CH	900	19.67	12.25	15	17.83	-9.34	18	17.58	-10.61	35	17.50	-11.02	78	17.50	-11.02
I.MK	85	23.45	0.00	-	-	-	8	23.92	2.00	14	23.70	1.07	29	23.55	0.43
II.MK	316	23.42	0.00	7	23.97	2.35	16	23.85	1.84	19	23.76	1.45	33	23.53	0.47
III.MK	390	19.60	0.00	14	20.78	6.02	18	20.51	4.64	27	20.19	3.01	41	19.84	1.22

solved twice, one having as objective the minimization of makespan and one the minimization of the changeovers.

Firstly, we use the suggested method with model M1 to examine the minimization of production makespan. Various insertion policies are tested, as shown in Table 3.2. As expected, a finer decomposition of the initial scheduling problem leads to lower CPU times, but also worse objective values. Given the computational time limitations, the best policy for this problem is to insert the product orders 20-by-20 in the optimization model. The less decomposed problem using a 40-by-40 order decomposition does not provide better solutions, since the time limit is reached, and a worse integrality gap is achieved. Finally, a monolithic approach cannot provide any integer solution within the allowed CPU time. The production schedule suggested and realized by the schedulers required a single 8-hour shift on Friday ($C_{max} \approx 104$), which is far worse than the generated schedule by the proposed solution strategy. Even when we apply a simple 1-by-1 insertion policy, we get results comparable to the solution proposed by the schedulers. However, this is achieved automatically in less than two minutes.

Next, we test the efficiency of the M2 model in combination with the suggested solution strategy, to address the changeover minimization objective. Again, we investigate various insertion policies, to decide on the most appropriate one, according to the imposed solution time limitations. In contrast, to the makespan minimization, products are now scheduled to minimize the total changeovers. Thus, no consideration of processing the orders as soon as possible exists. As a result, the fixed decisions on unit allocation and general precedence on products scheduled on previous iterations may lead to infeasible situations for the products yet to be scheduled. This occurs in the 1-by-1 insertion policy as shown in Table *3.3*. In order to avoid this situation, the problem must be less decomposed. The best results are generated when a 5-by-5 insertion is employed, in which a total changeover time of 42.7 hours is achieved, a solution that represents a 10-15% improvement compared to the one proposed by the schedulers. Inserting more products in each iteration could not further improve the objective since no integer solution is found within the allowed CPU time. In general, changeover minimization is a more difficult objective due to the utilization of the unit-specific general precedence model M2, which necessitates the further incorporation of immediate precedence variables and more sequencing constraints compared to model M1, thus leading to larger and more difficult problems.

Table 3.2: Comparison of insertion policies (makespan minimization)

Insertion policy	Objective (h)	CPU time (s)
1-1	104.6	94
2-2	97.6	120
5-5	96.0	159
10-10	95.3	221
20-20	94.4	356
40-40	94.6	900
Monolithic	-	900

Table 3.3: Comparison of insertion policies (changeover minimization)

Insertion policy	Objective (h)	CPU time (s)
1-1	Infeasible	-
2-2	43.5	89
5-5	42.7	850
10-10	-	900

An inevitable characteristic of the applied decomposition algorithm is that the size of the model continuously increases with each iteration. Let us consider the 20-by-20 policy for the makespan minimization problem, where in total five iterations of model M1 are solved. The number of binaries in the five MILP models generated is 9319, 18604, 29150, 43684 and 48144 accordingly. Consequently, the problems are, in general, getting harder and take more time to be solved. Main reason for this incremental tendency is the pairs of sequencing decisions that are not fixed, alongside the variables used for the feasibility constraints, which employ the discrete-time grid. In order to reduce the model sizes, we could fix all timing decisions (starting and completion times) after each iteration in the decomposition algorithm. However, this approach is less flexible and results in much worse scheduling decisions.

3.2.2.4 Industrial case II

In this case, we examine another problem instance of the same facility, however, this one represents a week during the most demanding production of the year. A total of

126 products must be scheduled, a number significantly larger than the one examined in instance I, which results in a scheduling problem of extremely high combinatorial complexity. The total demand is such that an overtime production is unavoidable; therefore, a scheduling horizon of 7 days is chosen. The demand of this case and all operational data, e.g., processing rates, product to line availability in each stage, sterilization times, changeovers, etc. are provided in Appendix B.

Model M1 is employed with a 20-by-20 insertion policy to propose a minimum makespan production schedule. The proposed solution strategy generates a near-optimal schedule in less than 10 minutes. A makespan of 133.1 hours is achieved, which compares favourably with the solution proposed by the schedulers. The executed weekly schedule demanded the uninterrupted operation of the plant throughout the weekend ($C_{max} \approx$ 148h), thus the proposed solution significantly reduces the overtime production. In Figure 3.5 the Gantt chart of the proposed schedule is illustrated for both the filling and sealing and packing stage. Notice that the labeller constraints are respected and at no point, a simultaneous operation of pairs of packing lines 1 - 2 and 5 - 6 occurs. Moreover, the number of utilized sterilizers never exceeds the total available resource installed in the plant (16 sterilizers) as depicted in Figure *3.4*.

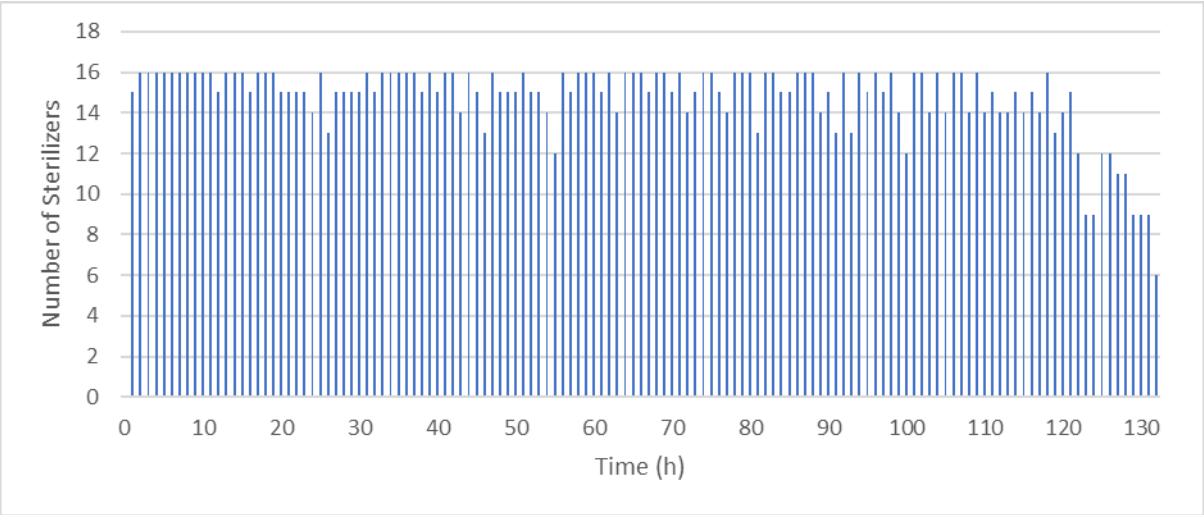

Figure 3.4: Number of sterilizers used at each time point of the scheduling horizon

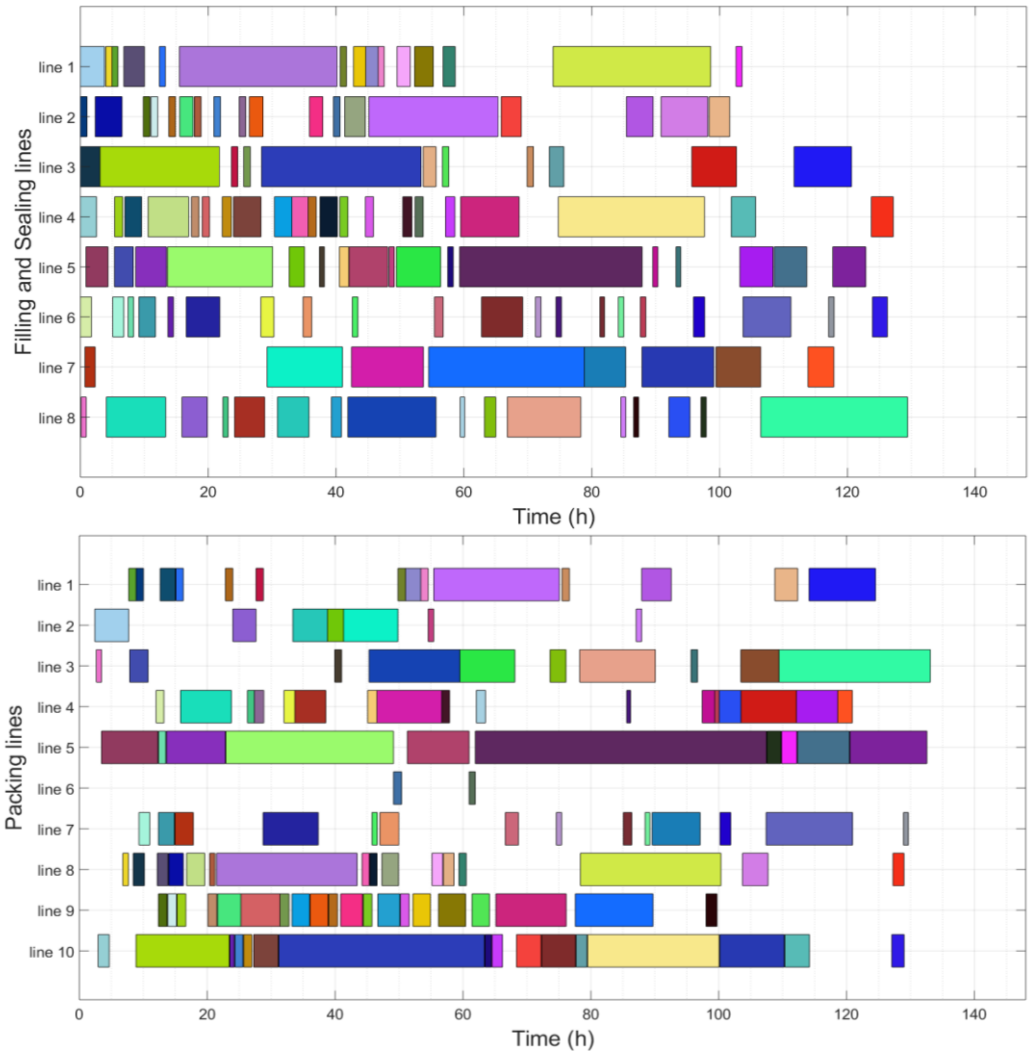

Figure 3.5: Gantt chart (makespan minimization)

Changeover minimization is considered for the industrial study case, using model M2 and a decomposition algorithm, in which products are inserted in a 5-by-5 fashion. The proposed schedule is generated in just under 15 minutes and the total changeovers required are reduced to 62.6 hours. Compared to the executed schedules an improvement of around 15% is accomplished, while the generated schedule has been fully validated by the production engineers of the plant. Figure *3.6* depicts the Gantt charts for both continuous stages. It is shown that choosing the minimal changeovers for each stage has a negative feedback on the total production time since it results in a worse synchronization between processes.

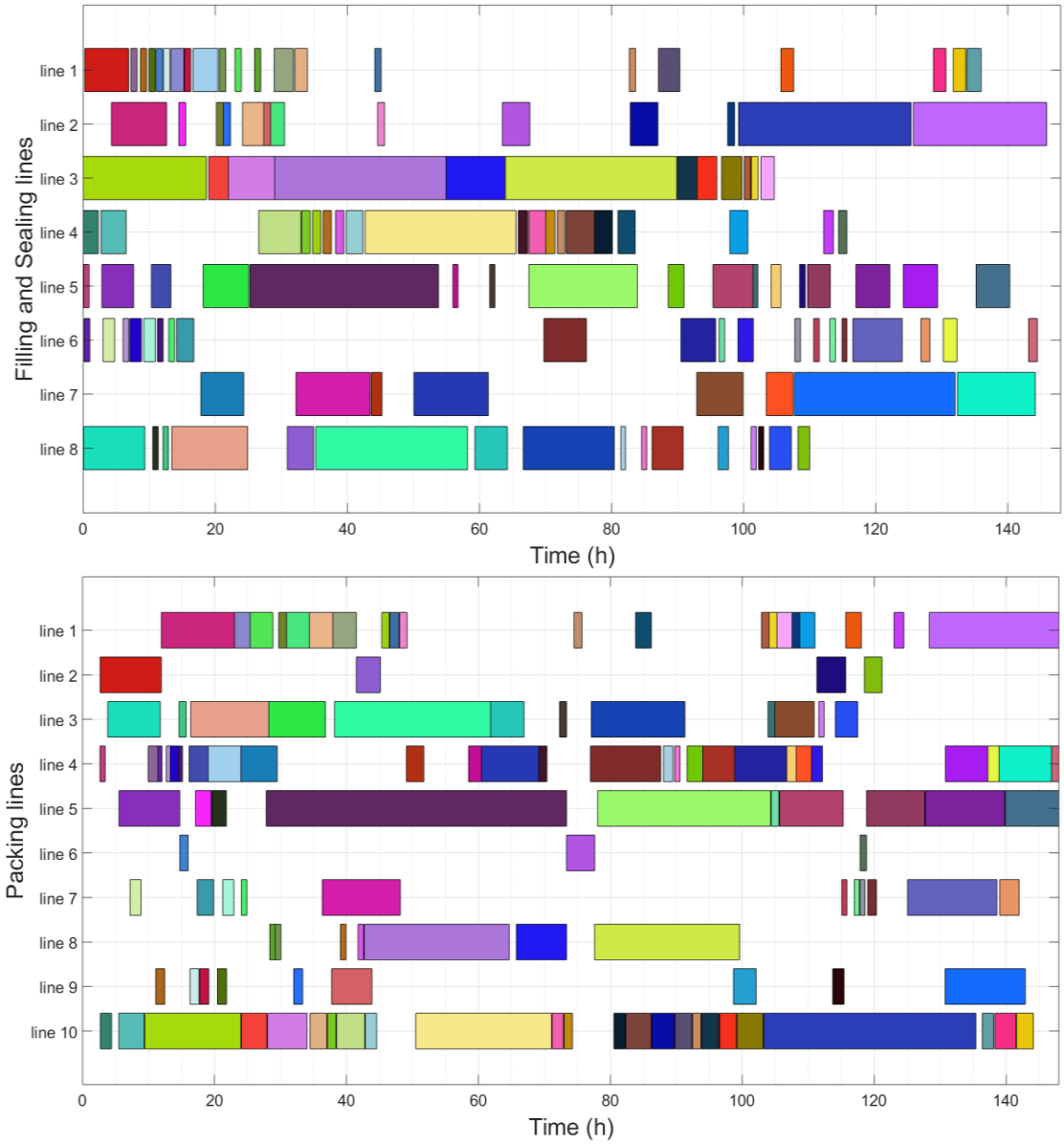

Figure 3.6: Gantt chart (changeover minimization)

3.3 General considerations

Prior to the development of an efficient scheduling solution for a real industrial case, two critical issues must be thoroughly considered. More specifically, the proper description of the scheduling problem at hand and the accuracy of the input data. If the specifics of the production process are not explicitly pre-defined or the given data are inaccurate, then the proposed methods result to solutions that cannot be practically applied to the real plant. Furthermore, data inaccuracies make the assessment of the model's efficiency extremely difficult or even impossible. In the specific industrial case,

both issues resulted to significant delays, mainly due to miscommunication reasons between the model developers and the production engineers. A representative example is the existence of the common labellers which became known to the model developers after months of work. Another issue was that some important parameters were initially not available at all. Therefore, the extraction of this information required a significant amount of work from the industrial partners' side. Through the constant collaboration between all partners, these issues were eventually resolved. In its final form, the developed model can depict the reality of the production process and propose realistic solutions, while all required data are now automatically provided by the plant's computer systems.

A direct comparison of the two mathematical frameworks is not meaningful for two main reasons. First and foremost, they consider different aspects of the industrial problem. Approach A considers a daily demand when a weekly demand is optimized in approach B. Moreover, the special labeller constraints cannot be incorporated in the first approach. Furthermore, changeover minimization is possible only when using approach B, while approach A provides detailed decisions for all processing stages. Secondly, approach B is clearly superior in terms of computational efficiency, since problem instances of similar if not higher complexity can be solved in just a fraction of the time required by approach A.

3.4 Conclusions

In this chapter, the optimal production scheduling problem of a large-scale, real-life food industry, for both makespan and total changeover time minimization, is considered. The overall scheduling problem is characterized by a significant combinatorial complexity. More specifically, the industrial facility is described by multiple production stages, each consisting of multiple parallel units, while both continuous and batch processes exist. Over 100 products must be processed within the scheduling horizon, resulting to a very large number of decisions to be made. To the best of our knowledge, a problem of such complexity has not been successfully solved in a reasonable computational time. In order to efficiently address this problem, the mathematical frameworks developed in Chapter 2 are utilized and their applicability and efficiency is illustrated. The two proposed mathematical frameworks can be

interchangeably used depending on the needs of the production engineers. Approach A is suitable for the cases where detailed scheduling decisions for the sterilization stage are required, the given demand is daily, and shutdowns are required at the end of each day. In all other cases approach B must be employed as it is computationally superior. A decomposition algorithm has been investigated for the efficient solution of the scheduling problem within a desired computational time limit. In the proposed methodologies, the products to be scheduled are optimized iteratively, according to a user-defined insertion policy. Moreover, the extraction of validated results for industrial cases that directly use real-life data by the ERP and MES of the plant, make the proposed strategies suitable for the development of a computer-aided scheduling tool, that will assist decision-makers to generate fast and near-optimal schedules. Finally, this chapter illustrates the successful implementation of an optimization-based method for the production scheduling of a real industrial problem, which is a step towards filling the existing gap between industrial reality and research.

Chapter 4

Optimal Production Planning and Scheduling in Breweries

4.1 Introduction

Beverage industrial facilities display production characteristics e.g., multiple mixed batch and continuous processes, an ever-expanding product portfolio, intermediate due dates, etc., which make the optimal production planning and scheduling of real-life industrial problems extremely challenging. Few contributions have addressed the production scheduling of the soft drink industry, using either optimization-based (Ferreira, Morabito, and Rangel 2009; Ferreira et al. 2012) or non-exact methods (Toledo et al. 2009). The generic optimal production scheduling problem for beverage industries can be addressed using the mathematical frameworks proposed in Chapter 2. However, the optimal production scheduling of breweries displays some special characteristics, which makes this optimization problem even more difficult, thus exceeding the capabilities of the previously presented solution strategies. The increased difficulty originates mainly from the very long lead times that characterize these industries. In particular, liquid preparation (fermentation and maturation) lasts from 3 up to 41 days, therefore, the synchronization of the various processing stages becomes a very difficult task. Moreover, an extended horizon must be examined, while both planning and scheduling decisions are required. Consequently, larger models are generated that must tackle the integrated planning and scheduling problem. Due to the size and complexity of such models, they become easily intractable when studying real-life industrial cases. As a result, only a handful of works have properly addressed the production planning and scheduling problem in breweries. Kopanos, Puigjaner, and Maravelias (2011) proposed a novel mixed discrete-continuous MILP model for the optimal production planning and scheduling of parallel continuous processes. The proposed model effectively addressed

industrial-scale problems of a real brewery, while it required very low computational times. However, their analysis focused solely on the bottling lines and was based on the assumption that the packing stage constitutes the production bottleneck, which does not always hold true. Baldo et al. (2014) were the first to study the optimal integrated production planning and scheduling problem of a beer production facility. They assumed that the production can be divided into two processing steps, liquid preparation, and bottling. Based on this valid simplification they developed a novel MIP model and proposed MIP-based heuristics in order to solve large-scale problems. Recently, Lee and Maravelias (2020) employed the general discrete and continuous algorithm (DCA) (Lee and Maravelias 2018) for the optimal production lot-sizing and scheduling of a large brewery. The authors modelled the beer production as a four-stage problem that consisted of four processing stages (brewing, fermentation, maturation and bottling) and were able to propose optimized schedules. Due dates were not modelled, rather monthly production targets were to be achieved and the main objective addressed was profit maximization.

The main contribution of this chapter is the development of a novel optimization-based solution approach for the integrated planning and scheduling problem of breweries. A new MILP model based on a mixed discrete-continuous time representation is developed. In order to reduce the size of the generated model, only the production bottlenecks of the process are modelled, while the considered horizon is divided into two sub-horizons. In the first one a detailed optimal production schedule is extracted, while in the second only planning decisions are considered. To the best of our knowledge the only model found in literature that can tackle such a process is proposed by Baldo et al. (2014). An extensive analysis is included that proves the superiority of the developed model both in solution quality and computational time. However, the large number of involved tanks, lines, and products and most importantly the large lead times, results to extremely complex models especially when dealing with real-life problems. Thus, the direct application of the developed model in industrially-sized cases leads to intractable models. Therefore, we propose a novel solution strategy that consists of a constructive and an improvement step. In the first an initial solution is generated that is then improved in the second step of the proposed algorithm. Finally, the suggested method is

successfully applied to an industrial case study provided by a large Greek beer production facility.

4.2 Problem Statement

Beer production is a complex process that comprises of multiple production steps that involve numerous shared resources. Any beer type consists of four main ingredients, in particular, water, malt (from barley grains), hop (responsible for the bitter taste of beer) and yeast (saccharomyces cerevisiae for ale beer or saccharomyces pastorianus for lager beer). The various beer products are diversified in terms of raw materials and the required processing time in each production step. Despite the distinct process required for each beer type, all products go through the same processing steps, which can be categorized into two main production stages, liquid preparation, and bottling (Figure 4.1).

Some breweries produce their own malt; therefore, a malting process is taking place prior to the brewing process. The malting process is divided into three subprocess; steeping, where the humidity of the grain is increased, germination, which transforms the grains into malt and finally drying in kiln, to remove most of the humidity from the malt. In this study we assume that the malt is a raw material that is ready to be brewed, therefore the malting process is not considered. In the liquid preparation stage two main processes take place, specifically, brewing and fermentation/maturation. The brewing process consists of several batch tasks, namely mashing, lautering, boiling, whirlpooling and cooling, that transform the raw materials into different worts. Mashing involves the addition of water into the prepared malt and the heating of the mixture, while in lautering the mixture is filtered from any solids. Then the hops are added, and the mixture is heated in the boiling process. Finally, the wort is filtered (whirlpooling) and quickly cooled (cooling). In the next processing step, the yeast is added into the cooled wort and the fermentation/maturation process begins. This subprocess constitutes one of the main production bottlenecks, since it lasts 3 to 41 days, depending on the type of beer produced. At this moment beer of a given wort type is obtained, referred to as bright beer. Finally, bright beer is transferred from the fermentation/maturation tanks to bright beer

tanks (BBTs), where it is filtered, diluted, and carbonated. At the end of the liquid preparation process the beer is referred to as ready beer or ready liquid.

Bottling is the last stage of the production process, where the ready liquid is bottled in cans, bottles, or kegs and then the final products are packed and palletized. Multiple subprocesses take place during the bottling process. First the returnable bottles are cleaned and sterilized, while cans and kegs are simply washed. Next the filling subprocess takes places, which is the main production bottleneck of the bottling stage. The products are then sealed and pasteurized in a bath of hot water to ensure that they are not infected by any harmful microorganisms. Finally, labelling, packing and palettizing takes place and the final products are loaded on a transport vehicle or stored in a warehouse.

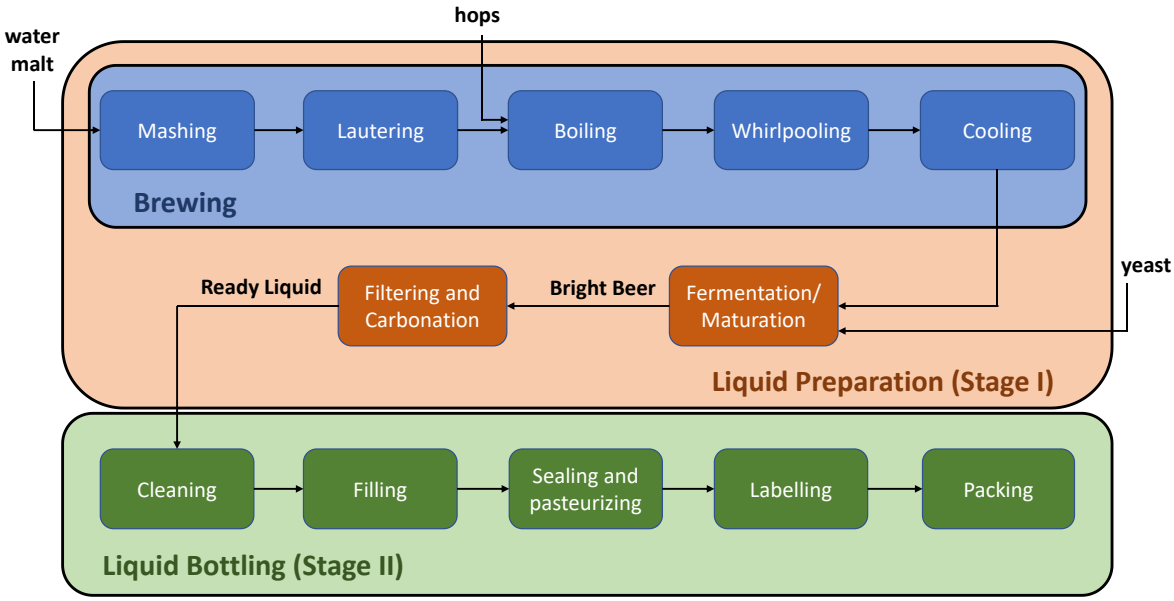

Figure 4.1: Description of the beer production process

The brewery industry, like most food and beverage industries, can be described as a make-and-pack industry, where in the initial stages the raw materials are processed based on a given production recipe and then are packaged in the desired final form. In order to efficiently address the optimal production planning and scheduling problem of breweries, only those processes that constitute the main bottlenecks of production are modelled. The most challenging task in the first stage is the proper utilization of the fermentation and maturation tanks. The rest of the subprocesses of this stage only take a

few hours, when the fermentation/maturation task requires a processing time that lasts multiple days, thus making it the bottleneck of the liquid preparation stage. Similarly, the limited capacity of the filling subprocess makes it the most difficult task of the second stage and therefore its production bottleneck. Moreover, the more ready liquid is bottled in the filling process, the faster the tanks empty and therefore become available to process a new batch of liquid. As a result, the beer production process is extremely simplified, leading to relatively small sized models, while containing all necessary information for the generation of feasible and optimal production schedules (Figure 4.2).

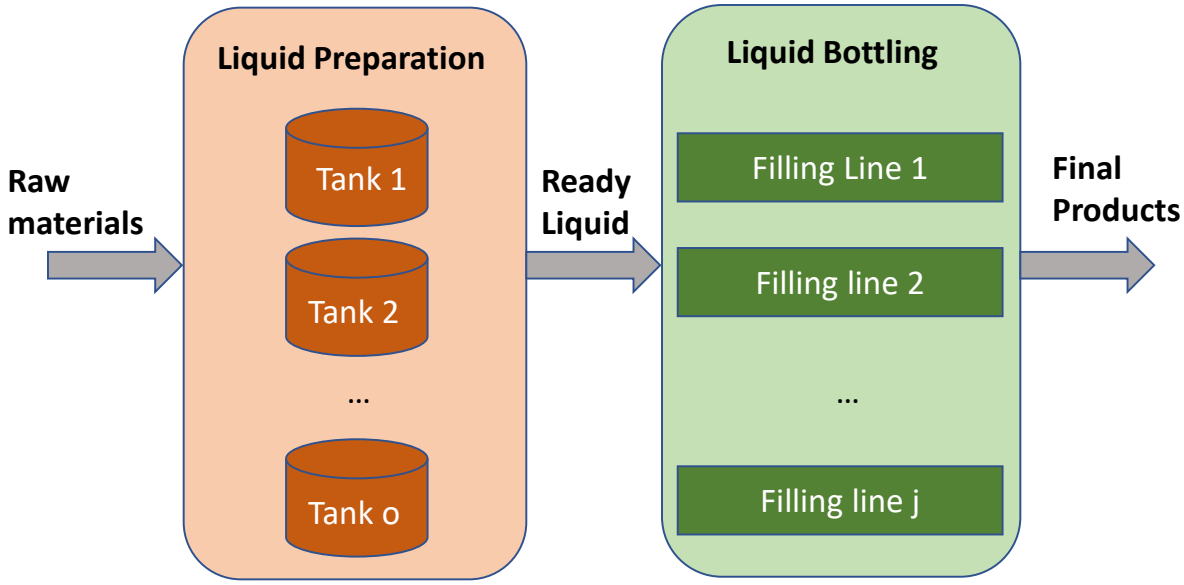

Figure 4.2: Simplified process description focusing on production bottlenecks

Based on the aforementioned simplifications, the brewery facility can be described as a multistage, multiproduct facility that combines both a batch (fermentation/maturation) and a continuous (filling) process with multiple parallel units. The first stage involves a number of tanks, which are non-identical in terms of capacity, but can process all liquids. In contrast, each filling line of the second stage can only process a specific subset of the final products, depending on the packing and bottling type of the line. Tanks can only prepare a single liquid at a time and likewise filling lines can only bottle a single product at a time. In terms of availability of connections, a tank can simultaneously supply multiple lines with ready liquid, however each line can receive ready beer from a single tank at a time. Furthermore, tanks must be cleaned in-between the fermentation/maturation process of two different batches, thus a sequence-

independent setup time is necessary. On the contrary, sequence dependent setup times for cleaning and/or machine adjustments are required in the filling lines, whenever a changeover of liquids and/or packages occurs. There are no intermediate storage vessels, however the ready liquid can be temporarily stored in the fermentation and maturation tanks.

The current industrial reality in most plants imposes the production plans and schedules to be generated manually by the decision makers. The large number of involved items (processing stages, units, and products) alongside the tight operational, logistical, and technical constraints to be considered result to an extremely complex problem. In addition, the long lead times require an extended planning horizon compared to other industries, while the generated schedules should ensure the proper synchronization of the liquid preparation and bottling stages. Thus, it is very difficult for the production engineers to consider the integrated planning and scheduling problem even using simple heuristics. In order to propose feasible schedules, the decision-making process is divided into two steps. First, the production plan for the sterilization and maturation tanks is generated. In this step the timing of all filling and emptying operations in each tank and the allocation of liquids into tanks is defined. The plans are determined for a monthly horizon based on the given demand and the capacity limitations of the units. At this point the goal of the production engineers is to utilize the tanks as much as possible while trying to reduce backlogs and maintain a relatively small inventory. Then the plan is thrown over the wall to the department responsible for production scheduling, which generates a feasible schedule for the filling lines. Here, the tank to filling line connections are determined (which tank will provide liquid to which line), and it is decided when will each filling process take place (timing) and at what order will every final product be processed (sequencing).

The decision-making procedure described above lacks efficiency since the two main production stages of the plant are considered separately without the employment of optimization-based methods. Therefore, the realized production plans and schedules are far from being optimal, resources are underutilized, productivity is decreased, and total profits are reduced. Thus, the efficient integration of both planning and scheduling decision is an area with great potential for improvement, that could be translated to significant benefits for the brewing industry. Main goal of this work is to develop an MILP-

based solution method for the integrated production planning and scheduling problem that provides near-optimal decisions in short computational times. The developed solution strategy can be the core of a computer-aided tool that facilitates the decision-making process and assists the production engineers of any brewery plant.

The problem under study can be formally stated as follows.

Given:

- A known planning horizon *H* divided into a set of time periods $t \in T$. The horizon is further divided into two subset of time periods, $t_1 \in T_1$ and $t_2 \in T_2$,($T = T_1 \cup T_2$). In the first precise production schedules are determined, while in the latter only production plans are generated.
- A set of fermentation/maturation tanks $o \in O$ and a set of filling lines $j \in J$.
- A set of liquids $l \in L$ to be prepared and a set of final products $i \in I$ that must be produced with the given horizon.
- The multidimensional set I_l that denotes whether product *i* contains liquid *l*.
- The mapping set I_j that defines the set of products *i* that can be processed on filling line *j*.
- All production related parameters, in particular, demand $\zeta_{i,t}$, liquid preparation time λ_l, filling rate for each final product $\rho_{i,j}$, capacity of each tank χ_o, and quantity of liquid required for a single unit of product *i*, $\pi_{i,j}$.
- A sequence-dependent setup for cleaning and/or machine changes necessary in the filling lines *j* whenever there is a changeover of production between two final products *i* and *i'*. Every changeover task requires a specific time $\gamma_{i,i',j}$.
- The cost coefficients associated with inventory σ_i, backlog β_i and changeover operations $\kappa_{i,i',j}$.

Determine:

- The planning decisions for the liquid preparation stage. More specifically, determine the filling and emptying operations in each tank as well as the material balance (amount of ready liquid) in each tank.
- The amount of liquid that is being transferred from each tank to each filling line.

- The allocation of products into filling lines, as well as the sequencing between products in each line and the completion time of each filling operation.
- The production amounts of final products as well as the product inventories and backlogs.

,so that an economic objective including inventory, backlog and changeover costs, is minimized. All data used are deterministic, meaning that any type of uncertainty is omitted in this study, while we assume that raw materials are always available. Resource limitations, such as manpower or utilities, e.g., cold water, electricity, are not considered. No intermediate storage vessels exist; however, the ready liquid can be stored in the fermentation and maturation tanks. We assume an instantaneous transfer of liquid between the two stages and that the fermentation/maturation process in a tank only starts at the beginning of a time period and is completed at the end of a time period.

4.3 MIP-based solution method

An MILP model is presented to efficiently address the integrated production planning and scheduling problem for a multistage multiproduct facility typically found in the brewing production process. The model is based on a precedence-based framework that utilizes a mixed discrete-continuous time representation, inspired by the works of Kopanos, Puigjaner, and Maravelias (2011) and Baldo et al. (2014). Operational and technical constraints, such as demand requirements and tank capacities, as well as specific characteristics of the production are incorporated to produce feasible plans that minimize the total production cost, which, in this study, comprises of the inventory, backlog and changeover cost terms. However, the high combinatorial complexity of the problem, especially when addressing large-scale industrial cases, is such that the direct application of known MILP solvers, e.g., CPLEX, GUROBI etc., results into low quality solutions. Moreover, computational times prohibitive for any industrial application are required. Therefore, we also introduce a two-step decomposition strategy, consisting of a constructive and an improvement step, in order to promptly generate feasible and near-optimal plans.

4.3.1 MILP model

The detailed modelling of all processing steps of the brewery facility would result to large and complicated models. Therefore, only the main production bottlenecks are considered, in particular, the fermentation/maturation process in the liquid preparation stage and the filling process in the liquid bottling stage. Thus, the facility at hand is reduced to a two-stage multiproduct one. This make-and-pack type of process is very common in food and beverage facilities. Therefore, an abundance of various techniques that can optimally solve this type of problems can be found in the literature. However, beer production displays characteristics that significantly differentiate them to other production processes. Compared to other food and beverage industries, the preparation step (fermentation/maturation in the case of breweries) requires a large processing time that spans from some days to multiple weeks, resulting in large production lead times. Hence, planning must be considered in synchronization with short term scheduling since product preparation lasts more than the usual scheduling horizon (one week). In case of optimizing just the scheduling decisions of the filling process (Stage 2), there is a high risk of generating schedules that overestimate the capacity of the fermentation/maturation tanks (Stage 1), thus leading to an infeasible solution.

In order to address this optimization problem, an MILP model has been developed, that employs a mixed discrete-continuous time representation. The discrete time grid has a period length of one day and is used to seamlessly monitor the production, inventory, and backlog levels of both stages. A lot-sizing model is introduced for the planning decisions of both stages, that considers the given processing times of the tasks and the capacity of the units involved. Within each time period a continuous representation of time is utilized, and constraints inspired by the immediate precedence framework are incorporated to determine the sequencing decisions in the liquid bottling stage (Stage 2). Note that sequencing decisions are not required in the first stage, since it does not involve any sequence-dependent setup times. The planning horizon is divided into two sub-horizons. In the first one (T_1), both planning and scheduling decisions are considered, while in the second one (T_2) a coarser optimization is done, than only determines the lot-sizing and unit utilization decisions. Figure 4.3 portrays the employed time grid, as well as the decisions that are made for each stage and in each sub-horizon. The orange oval shape contains the considered decisions for Stage 1, while the green oval shape displays

the determined decisions for Stage 2. Blue-coloured text denotes the planning decisions, while red-coloured text signifies the scheduling decisions. The intersection of the two shapes encloses the decisions that connect the two stages, specifically, the amount of liquid that is transferred from the tanks to the filling lines.

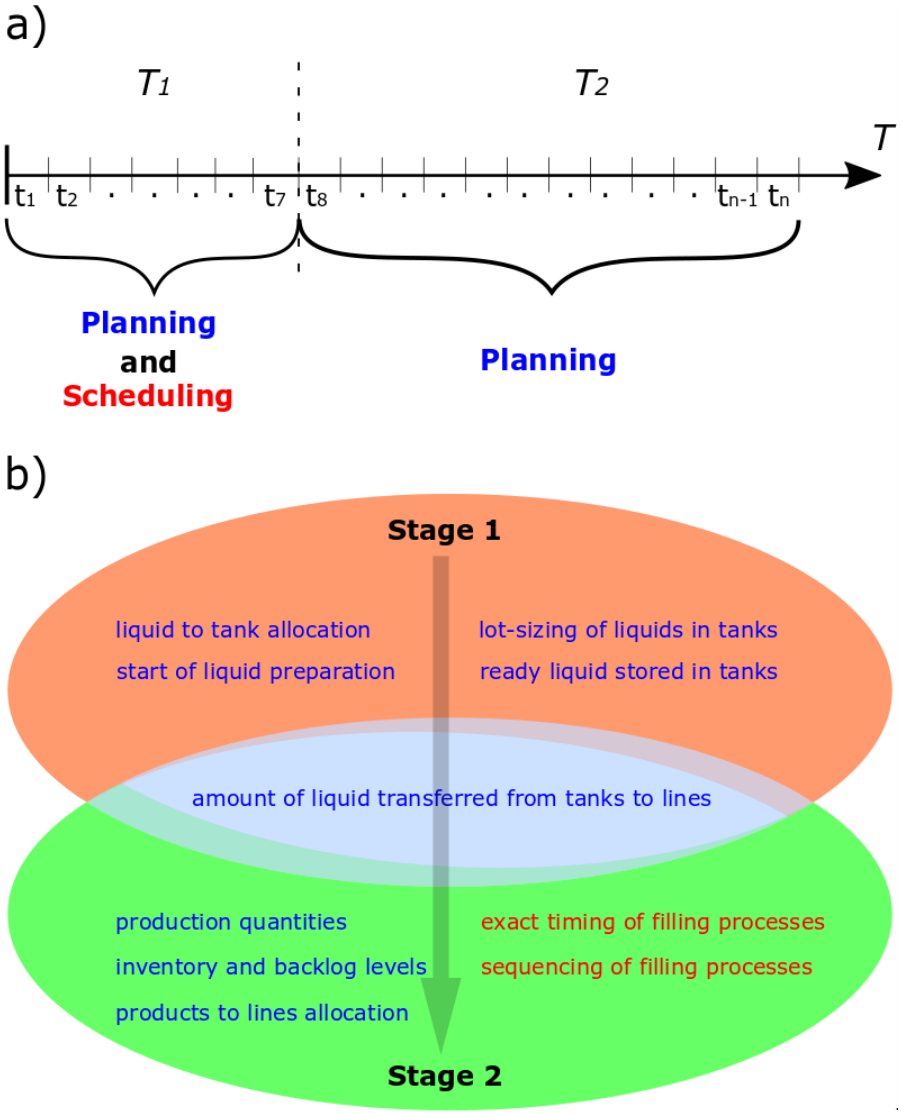

Figure 4.3: a) Time representation and description of sub-horizons, b) considered planning and scheduling decisions in each stage

Let us describe the main decision variables of the developed model for the integrated planning and scheduling problem in breweries. The liquid is transferred into the tanks and the fermentation/maturation process starts. When the required processing time λ_l passes, then an amount $L^P_{o,l,t}$ of liquid gets ready. Binary variable $Y^1_{o,l,t}$ denotes that liquid l in tank o gets ready in time period t. The ready liquid is either used on filling lines

j to produce items i in period t ($L^T_{o,j,i,t}$) or is stored in tank o for future production ($L^S_{o,l,t}$). In case the ready liquid is used to produce items on filling lines, then an amount of item i ($Q_{o,i,j,t}$) is processed on filling line j in period t made of liquid fed by tank o. This amount is used to satisfy the demand on the current or previous time periods ($t' \leq t$) or is stored to meet future demand of item i ($t' > t$). Note that the outputs of Stage 1 (liquid preparation) are the inputs of Stage 2 (liquid bottling), so the production in the filling lines takes place only when there is available ready liquid to be fed from the fermentation/maturation tanks. In terms of scheduling decisions, unit allocation variables ($Y^2_{i,j,t}$) are used to denote that a product i is processed in line j in time period t and two sets of immediate precedence variables ($X_{i,i',j,t}$ and $\bar{X}_{i,i',j,t}$) are employed to indicate direct precedence of tasks. The first is enabled whenever there is direct precedence of production between two final products, i and i', in line j in the same period t, while the latter indicates precedence of filling tasks between consecutive periods. Continuous variables $U_{j,t}$ and $\bar{U}_{j,t}$ are used to properly model changeovers between tasks in consecutive time periods. Lastly timing variables $C_{i,j,t}$ are employed to signify the completion of a filling task of product i in time period t. An overview of the main decision variables is illustrated in Figure 4.4.

Next, we present the developed model, categorizing the constraints based on the production stage and the types of decisions they subject to. To facilitate the presentation of the model, we use lowercase Latin letters for indices, uppercase Latin letters for variables and lowercase Greek letters for parameters. From now on we will refer to this model as GEG.

Stage 1 (Liquid preparation)

In the first stage, the constraints are mainly responsible for properly modelling the lot-sizing of the fermentation/maturation tanks. More specifically, they must guarantee that the processed liquid lots do not exceed the capacity of the fermentation tanks and that the liquids remain in the tanks at least for the required fermentation/maturation processing time.

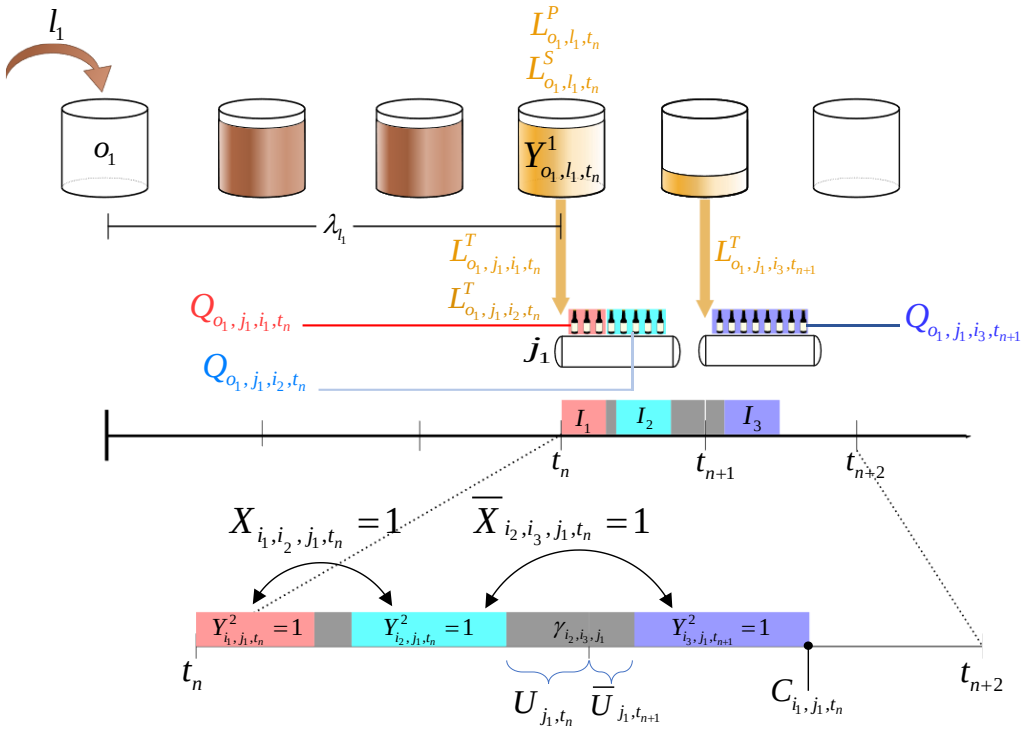

Figure 4.4: Description of main decision variables

Constraints (4.1) ensure that if a liquid gets ready in time period t ($Y^1_{o,l,t} = 1$), then no ready liquid is stored in the tank during the previous λ_l time periods. During this period the fermentation/maturation process of the liquid takes place. In order to have an amount $L^P_{o,l,t}$ of ready liquid in time period t, the tank must be empty in time period $t - (\lambda_l + 1)$, so that it can receive the liquid to initiate its preparation (fermentation/maturation) process. Constraints (4.2) are introduced to guarantee that at most one batch of liquid gets ready in a tank within a time segment equal to the fermentation/maturation time. Finally, constraint set (4.3) imposes the upper bound on the amount of liquid getting ready based on the available capacity of the fermentation/maturation tanks.

$$\sum_{l'} \sum_{t'=t-\lambda_{l'}-1}^{t-1} L^S_{o,l',t'} \le M \cdot (1 - Y^1_{o,l,t}) \qquad \forall o,l,t \qquad (4.1)$$

$$\sum_{l} \sum_{t'=t-\lambda_{l'}}^{t} Y^1_{o,l,t'} \le 1 \qquad \forall o,t \qquad (4.2)$$

$$L^{P}_{o,l,t} \leq \chi_o \cdot Y^{1}_{o,l,t'} \qquad \forall o,l,t \qquad (4.3)$$

Stage 1 and Stage 2

Constraints (4.4) are responsible for connecting the decision variables of the two stages, while they monitor the liquid balance between them. More specifically, they state that the stored amount of liquid *l* in tank *o* in time period *t* ($L^{S}_{o,l,t}$) is equal to the stored amount in the previous period plus the amount of liquid getting ready in period *t* ($L^{P}_{o,l,t}$), minus the liquid that is transferred to the filling lines.

$$L^{S}_{o,l,t} = L^{S}_{o,l,t-1} - \sum_{i \in I_j} \sum_{j \in J_i} L^{T}_{o,j,i,t} + L^{P}_{o,l,t} \qquad \forall o,l,t \qquad (4.4)$$

Stage 2 (Liquid bottling)

The second stage requires a more detailed model since additional to the lot-sizing and unit allocation constrains it also considers the timing and sequencing decisions for the filling lines. In order to generate the required modelling constraints, the immediate precedence framework is employed within a mixed discrete-continuous time representation (Kopanos, Puigjaner, and Maravelias 2011).

Material balance constraints

The material balances for every final product are imposed by constraint set (4.5). At the end of each time period *t*, the inventory ($S_{i,t}$) and backlog ($B_{i,t}$) are monitored based on the daily production, demand and the inventory and backlog levels in the previous time period *t-1*. The number of products *i* that use liquid fed by tank *o* and are processed in line *j* and time period *t* is expressed by constraints (4.6).

$$S_{i,t} - B_{i,t} = S_{i,t-1} - B_{i,t-1} + \sum_{j \in J_i} \sum_{o} Q_{o,j,i,t} - \zeta_{i,t} \qquad \forall i,t \qquad (4.5)$$

$$Q_{o,j,i,t} = \pi_{i,l} \cdot L^{T}_{o,j,i,t} \qquad \forall o,j,i \in I_j,t \qquad (4.6)$$

Line utilization constraints

The constraints below introduce the line utilization variable, which is enabled, i.e., $V_{j,t} = 1$, when a filling line *j* is used in time period *t*. In particular, constraints (4.7) ensure

that a filling line *j* is utilized in time period *t*, if at least one product *i* is processed in this line and time period. Furthermore, constraint set (4.8) force the unit utilization variable to take a value of 0, in case no product is processed in that particular line and time period t.

$$V_{j,t} \geq Y^2_{i,j,t} \qquad \forall i, j \in J_i, t \in T \qquad (4.7)$$

$$V_{j,t} \leq \sum_i Y^2_{i,j,t} \qquad \forall i, j \in J_i, t \in T \qquad (4.8)$$

Sequencing and timing constraints

The binary variable $X_{i,i',j,t}$ is introduced to define the immediate precedence relation between two products *i* and *i'* in line *j* and time period *t*. Moreover, we employ the binary variables $W^F_{i,j,t}$ and $W^L_{i,j,t}$, which define the first and last product being processed in line *j* and time period *t* accordingly. Constraints (4.9) and (4.10) guarantee that if a product is processed in filling line *j* and time period *t* ($Y^2_{i,j,t} = 1$), it will have at most on predecessor and one successor. In case product *i* is processed first in line *j* and time period *t*, then it has no predecessor and similarly if it is processed last, it has no successor. Finally, tightening TSP-based constraints (4.11) are introduced, which specify the exact number of active sequencing variables. More specifically, they ensure that if line *j* is used in time period *t*, then the total number of enabled sequencing variables is equal to the number of products being processed minus 1. Otherwise, all sequencing variables for that specific line and time period are forced to zero.

The timing considerations are imposed by the next two constraints. Constraint set (4.12) guarantees that the filling process for a product *i'* that is processed right after product *i,* must be completed after the completion of product *i* plus the required processing and changeover time. The constraint is formulated as a big-M constraint, meaning that when the succession relation is absent ($X_{i,i',j,t} = 0$), then the constraint becomes inactive. The big-M parameter used is ω, which corresponds to the daily time availability of each filling line. In this particular study this is assumed to be 24 hours. Furthermore, constraints (4.13) are employed to ensure that the filling process for each product is completed after the required processing time.

$$\sum_{i'\neq i,i'\in I_j} X_{i',i,j,t} + W^F_{i,j,t} = Y^2_{i,j,t} \qquad \forall i,j\in J_i, t\in T_1 \qquad (4.9)$$

$$\sum_{i'\neq i,i'\in I_j} X_{i,i',j,t} + W^L_{i,j,t} = Y^2_{i,j,t} \qquad \forall i,j\in J_i, t\in T_1 \qquad (4.10)$$

$$\sum_{i\in I_j}\sum_{i'\neq i,i'\in I_j} X_{i,i',j,t} + V_{j,t} = \sum_{i\in I_j} Y^2_{i,j,t} \qquad \forall j\in J_i, t\in T_1 \qquad (4.11)$$

$$C_{i',j,t} \geq C_{i,j,t} + \sum \rho_{i,j}\cdot Q_{o,j,i,t}\cdot X_{i,i',j} - \omega\cdot(1-X_{i,i',j,t}) \qquad \forall i,i'\neq i, t\in T_1,\ j\in(J_i\cap J_{i'}) \qquad (4.12)$$

$$C_{i,j,t} \geq \sum_o \rho_{i,j}\cdot Q_{o,j,i,t} \qquad \forall i,j\in J_i, t\in T_1 \qquad (4.13)$$

Sequencing constraints between adjacent periods

In order to model changeover operations between processes that take place in adjacent periods, we introduce binary variables $\bar{X}_{i',i,j,t}$. Constraints (4.14) and (4.15) state that this variable is active only for the products *i'* that are processed first in line *j* and in time period *t* and products *i* that are processed last in line *j* and time period *t-1*. Furthermore, continuous, and positive variables $U_{j,t}$ and $\bar{U}_{j,t}$ are introduced, to represent time fractions of changeover operations between adjacent periods. Constraints (4.16) are imposed to facilitate the proper incorporation of these newly introduced variables in the model. Assume there is changeover that starts in period *t-1* and finishes in period *t*. Then the fraction of the changeover operation that is performed in time period *t-1* is represented by$U_{j,t-1}$, while the time fraction of the changeover that takes place in time period *t* is modelled by $\bar{U}_{j,t}$. Of course, the addition of these times must equal the total changeover time $\gamma_{i,i',j}$.

$$W^F_{i,j,t} = \sum_{i'\neq i,i'\in I_j} \overline{X}_{i',i,j,t} \qquad \forall i,j\in J_i, t\in T_1 \qquad (4.14)$$

$$W^L_{i,j,t-1} = \sum_{i'\neq i,i'\in I_j} \overline{X}_{i,i',j,t} \qquad \forall i,j\in J_i, t\in T_1 : t>1 \qquad (4.15)$$

$$\overline{U}_{j,t} + U_{j,t-1} = \sum_{i \in I_j} \sum_{i' \neq i, i' \in I_j} \gamma_{i,i',j} \overline{X}_{i,i',j,t} \qquad \forall j \in J, t \in T_1 : t > 1 \qquad (4.16)$$

Time availability constraints

Constraints (4.17) bound the operations in a filling line, based on the available production time. In particular, the summation of the changeover times, either within the same time period or between adjacent time periods, and the total processing time of all products being processed, must be less than the total available production time of the line. Note that all sequencing constraints are specified only for those subperiods that belong to the planning and scheduling sub-horizon ($t \in T_1$).

$$\overline{U}_{j,t} + U_{j,t-1} + \sum_{i \in I_j} \sum_{o} \rho_{i,j} \cdot Q_{o,j,i,t} + \sum_{i \in I_j} \sum_{i' \neq i, i' \in I_j} \gamma_{i,i',j} X_{i,i',j,t} \leq \omega \qquad \forall j, t \in T_1 : t > 1 \qquad (4.17)$$

Lot-sizing constraints

Finally, constraints (4.18) and (4.19) bound the production in the liquid bottling stage based on the given processing rates for each product and the available daily production time for each line. Note that in contrast to the timing and sequencing constraints, lot-sizing constraints are constructed for all time periods of the given horizon.

$$\sum_{o} Q_{o,j,i,t} \leq \frac{\omega}{\rho_{i,j}} \cdot Y^2_{i,j,t} \qquad \forall i, j \in J_i, t \in T \qquad (4.18)$$

$$\sum_{o} \sum_{i \in I_j} \rho_{i,j} \cdot Q_{o,j,i,t} \leq \omega \qquad \forall j \in J, t \in T \qquad (4.19)$$

Objective

The overarching goal of the optimization problem is to minimize the total production costs, which is modelled by three cost terms, inventory, backlog costs and changeover cost. The changeover cost term is only defined for the subperiods of the

planning and scheduling horizon ($t \in T_1$) since sequencing decisions are considered only for these time periods.

$$\textit{minimize} \quad \sum_{i}\sum_{t}(\sigma_i \cdot S_{i,t} + \beta_i \cdot B_{i,t}) + \sum_{i}\sum_{i',i'\neq i}\sum_{j\in(J_i \cap J_{i'})}\sum_{t\in T_1}\kappa_{i,i',j}(X_{i,i',j,t} + \overline{X}_{i,i',j,t}) \tag{4.20}$$

4.3.2 MILP-based solution strategy

In the previous subsection, we presented a new MILP model for the two-stage planning and scheduling problem of beer production facilities. Despite the efficiency of the presented model, the direct application of commercially available MIP solvers requires large computational effort, that may lead to increased solution times and suboptimal production plans. This is especially noticeable when dealing with real-life industrial applications, since brewery facilities are characterized by numerous fermentation/maturation tanks, filling lines, liquids, and final products. Consequently, the industrially-sized problems result in intractable case studies, which is unacceptable, since the developed solution method must always propose a production plan, even if it is suboptimal. Moreover, the industry works on a very tight schedule, therefore strict time limitations are imposed to any proposed solution. To ensure the viability of the proposed method as a computer-aided tool that can be a part of the any facility's IT infrastructure, it must provide solutions in computational times accepted by the industry. Thus, to satisfy these prerequisites a decomposition strategy is employed that guarantees the generation of a near-optimal production plans and reduces the combinatorial complexity of the optimization problem. A two-step decomposition technique, consisting of a constructive and an improvement step, is proposed. In the first part, an initial good solution is promptly generated, while in the second part an iterative method is used to improve the initial solution. The following subchapters describe the developed solution algorithm in detail.

4.3.2.1 Constructive step

In order to generate a feasible and good initial solution, a spatial decomposition approach is introduced, where the two production stages are considered independently.

Main goal of this method is to disaggregate the binary decisions of each stage, thus decrease the complexity of the initial model. We end up with two MILP-subproblems, one for Stage 1 (GEG_S1) and one for Stage 2 (GEG_S2), which are solved in that order. More specifically, GEG_S1 is solved to determine the decisions related to the fermentation/maturation tanks (in which tank will the liquids be prepared, when they are going to be ready and the corresponding amount that will be ready during the given horizon). Then this information is used in GEG_S2 to optimize the planning and scheduling decisions of the filling lines and finally generate the production plan for the whole process. The order in which the models are solved (first for Stage 1 and then for Stage 2) has been decided since the alternative (first GEG_S2 and then GEG_S1) could potentially lead to infeasibilities. This may occur due to an overestimation in the capacity of resources of the first stage. The productions plans for the filling lines generated by GEG_S2 are inapplicable in case the required amount of ready liquid exceeds the available capacity of the tanks in the first stage. On the other hand, this is not an issue in the suggested solution strategy since Stage 2 is more flexible than Stage 1. Due to the natural flow of material in the problem at hand and the capability of storing or backlogging final products, the filling lines can always adapt to the production plans of the fermentation/maturation tanks. This is crucial since the proposed solution method and possible future core of a computer-aided tool must ensure the generation of production plans and schedules for any possible case that could occur in the industrial facility. So, the constructive step is further split into two steps. The first one focusing on Stage 1 and the second on Stage 2.

Sub-step 1 (Stage 1)

To develop the model for the liquid preparation stage, we utilize a subset of the constraints from model GEG. Despite our emphasis on the first stage, we must also consider some of the constraints related to the liquid bottling stage. It is essential to include this information in order to avoid the generation of bad production plans that would lead to increased inventory and backlogging costs. If we ignore the incorporation of this information in the model, we could even end up to infeasible production plans. For example, if we do not consider the processing capability of the filling lines, then the model could impose a tank filling plan that prepares an amount of liquid that overwhelms the filling lines. So, the tanks could not be emptied in time and could not be ready for the

initiation of the fermentation/maturation process of the next batch, thus making the generated plan infeasible.

The goal of this model is to determine the tank filling operations by minimizing the potential inventory and backlogging costs (4.21). Constraints (4.1) – (4.3) are included to ensure that the operational constraints for the first stage are considered. Constraint set (4.4) must be incorporated in the model to properly model the interaction of liquid between Stage 1 and Stage 2. Furthermore, constraints (4.5) are necessary in order to monitor the inventory and backlog levels based on the given demand and optimized production. Finally, constraints (4.18) and (4.19) are responsible for providing the capacity information of the filling lines, in order to avoid infeasible solutions. The optimized planning decisions for the tanks, in particular the time period in which each liquid l gets ready in tank o and time period t ($Y^1_{o,l,t}$) and the corresponding amount ($L^P_{o,l,t}$), are saved in parameters $\hat{Y}^1_{o,l,t}$ and $\hat{L}^P_{o,l,t}$ respectively, to be later used in the second sub-step of the constructive step.

GEG_S1

$$minimize \quad \sum_i \sum_t (\sigma_i \cdot S_{i,t} + \beta_i \cdot B_{i,t}) \tag{4.21}$$

$$s.t. \quad \text{(4.1) - (4.5), (4.18), (4.19)}$$

Sub-step 2 (Stage 2)

In the next step, the proposed method solves model GEG_S2 for the second stage considering the solution of GEG_S1. In particular, it receives the optimized decisions that determine when a liquid gets ready and the respective amount. This information is respected in the model by incorporating constraints (4.22) and (4.23). More specifically, constraint set (4.22) ensures that a liquid gets ready only at the time imposed by the solution of the first sub-step ($\hat{Y}^1_{o,l,t} = 1$) and guarantees that the capacity limitations of the tanks are not violated. Note that the binary decision for the timing of the filling plan is fixed to be equal to the solution given by the previous step ($Y^1_{o,l,t} = \hat{Y}^1_{o,l,t}$). On the contrary the amount that gets ready is reoptimized in this step to increase the flexibility

of the proposed method. Of course, the respective non-negative variable is lower bounded by the solution of the previous step, so that the tank filling plans generated by GEG_S1 are respected. Additionally, constraints (4.23) guarantee that the tank will be empty and ready to receive the liquid and that the liquid will solely occupy the tank during the fermentation/maturation process. Furthermore, constraint (4.4) from model GEG is added to ensure that a production in the filling lines occurs only if there is ready liquid available. Moreover, we include all constraints related to the second stage (4.5) - (4.19). Finally, the objective of the model is to minimize the total production cost (inventory, backlog, and changeover costs).

GEG_S2

$$\textit{minimize} \quad \sum_{i}\sum_{t}(\sigma_i \cdot S_{i,t} + \beta_i \cdot B_{i,t}) + \sum_{i}\sum_{i',i'\neq i}\sum_{j\in(J_i\cap J_{i'})}\sum_{t\in T_1}\kappa_{i,i',j}(X_{i,i',j,t} + \overline{X}_{i,i',j,t}) \tag{4.20}$$

$$s.t. \qquad \hat{L}^P_{o,l,t}\cdot\hat{Y}^1_{o,l,t} \le L^P_{o,l,t} \le \chi_o \cdot \hat{Y}^1_{o,l,t} \quad \forall o\in O, l\in L, t\in T \tag{4.22}$$

$$\sum_{l'}\sum_{t'=t-\lambda_{l'}-1}^{t-1} L^S_{o,l',t'} \le M\cdot(1-\hat{Y}^1_{o,l,t}) \quad \forall o\in O, l\in L, t\in T \tag{4.23}$$

(4.5) - (4.19)

4.3.2.2 Improvement step

An iterative method is used to further improve the initial feasible solution generated in the constructive step. A number of improvement operators based on the fix-and-optimize heuristic are introduced, similar to the approach proposed by Baldo et al. (2014). The main idea of the fix-and-optimize heuristic is to define subsets of the model's binary variables, relax and re-optimize them, in the search for a better solution. Thus, two disjunctive subsets of the model's binary variables B_v are generated. The first one defines, which binary variables are relaxed B_v^R, and the second denotes the subset of binary variables whose values remain fixed B_v^F. As a result, an MILP subproblem is created that considers only a small portion of the initial problem. Therefore, each subproblem can be

solved to optimality in relatively small CPU times. In case the objective of the new solution is better, than the best solution found, the binary variables are updated, otherwise, the best solution found so far is kept. Note that all continuous variables are relaxed since they do not significantly increase the complexity of the model. This procedure is repeated through an exhaustive iterative approach that ensures that all subsets of binary variables are visited. A runtime limit is set to avoid prohibitive computational times that would constitute the application of the method impractical. We use the model presented in section 4.3.1, in order to address the integrated planning and scheduling problem of the whole production process.

Algorithm. Pseudocode of fix-and-optimize heuristic

Given the initial solution of the constructive step S^C with objective value $F(S^C)$
Define the number of iterations required to visit all subsets (k)
Define the computational limit (*limit*)
$iter = 0$
$S^{best} = S^C$
While ($CPU \leq limit \; and \; iter \leq k$) **do**
    k=k+1
    Define subsets B_v^R and B_v^F according to defined rules
    Solve generated MILP-subproblem (S^{new})
    If ($F(S^{new}) < F(S^{best})$**) then**
        Update binary variables
        $F(S^{best}) = F(S^{new})$
    end-if
end-while

Four improvement operators based on the aforementioned heuristic framework are employed. These operators are differentiated by the way they partition the problem's binary variables to form the various MILP-subproblems that will be solved iteratively. The rules used to define the subsets of the fix-and-optimize heuristic are based on temporal and/or spatial decomposition of the initial problem.

The fix-and-optimize forward (FO_F) operator employs a time decomposition scheme that starts at the beginning and ends at the end of the planning horizon (Figure

4.5a). In each iteration the binary variables of both stages are released for a specific number of time periods. In other words, the production plan is reoptimized for a partition of time. The length of this partition is equal to the maximum duration of fermentation and maturation of the involved liquids $max\{\lambda_l\}$. The algorithm then moves to the next time partition. The step of this movement is equal to the minimum duration of the fermentation and maturation process $min\{\lambda_l\}$. So, in case $max\{\lambda_l\} \neq min\{\lambda_l\}$ overlapping occurs, meaning that in each MILP-subproblem we include some of the decision variables of the previous iteration. This procedure continues until all variables have been revisited and reoptimized. The fix-and-optimize backward (FO_B; Figure 4.5b) operator is similar to FO_F, with the only difference being that the iterative procedure starts at the end of the horizon and finishes at the beginning.

The next two improvement operators FO_F21 (Figure 4.5c) and FO_B21 (Figure 4.5d) employ a bi-level temporal and spatial decomposition strategy. Their main difference to the first two operators is that in each iteration the binary variables of only one stage are relaxed, in particular first the ones of Stage 2 and then the ones of Stage 1.

Figure 4.6 illustrates a general overview of the proposed solution strategy for the optimal production planning and scheduling problem for beer production facilities. First an initial good and feasible solution is constructed, by disaggregating the decisions of the two processing stages. GEG_S1 is employed to solve the problem of Stage 1, and then sends the relevant information to GEG_S2, which in turn is solved to consider the second stage and generate the solution of the constructive step. This solution is then fed to the improvement step, where a set of improvement operators based on the fix-and-optimize heuristic are applied. As a result, we can consider large-scale industrial cases and generate near-optimal production plans in reasonable computational times.

4.4 Computational analysis

In this section numerous case studies are examined in order to evaluate the efficiency of the proposed model and solution strategy. Moreover, we illustrate the applicability of the developed solution method in real-life situations by considering a large-scale, real-life industrial problem of a brewing facility in Greece. In all presented case studies, the planning horizon is 42 days, while the scheduling decisions is a week. All

models and solution algorithms were developed using the GAMS 31.1 interface (Brooke et al. 1998) and all problem instances were optimally solved using CPLEX 12.0 in a PC equipped with an Intel Core i7 @3.4GHz CPU and 16 GB of DDR4 RAM.

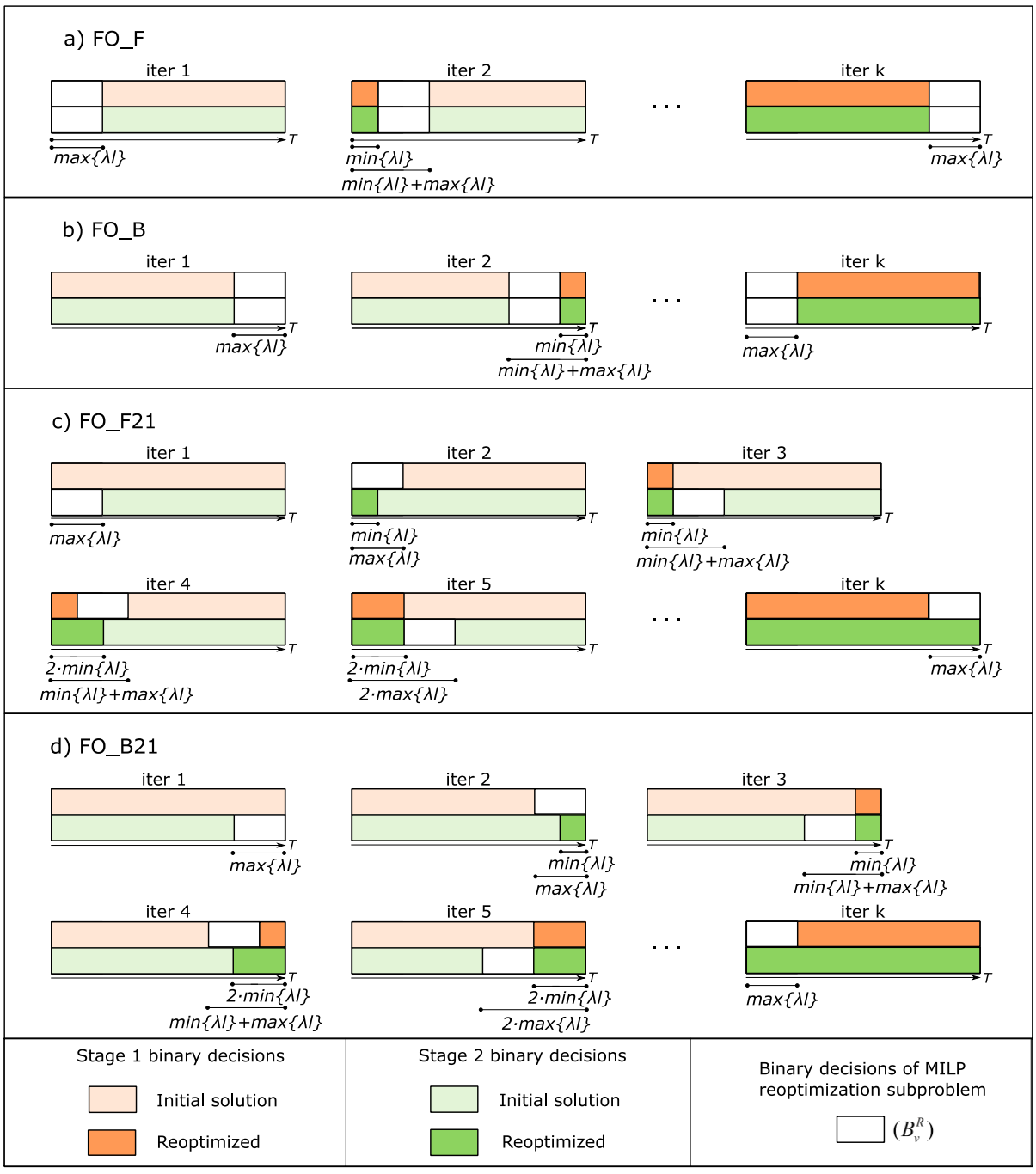

Figure 4.5: Fix and optimize improvement operators

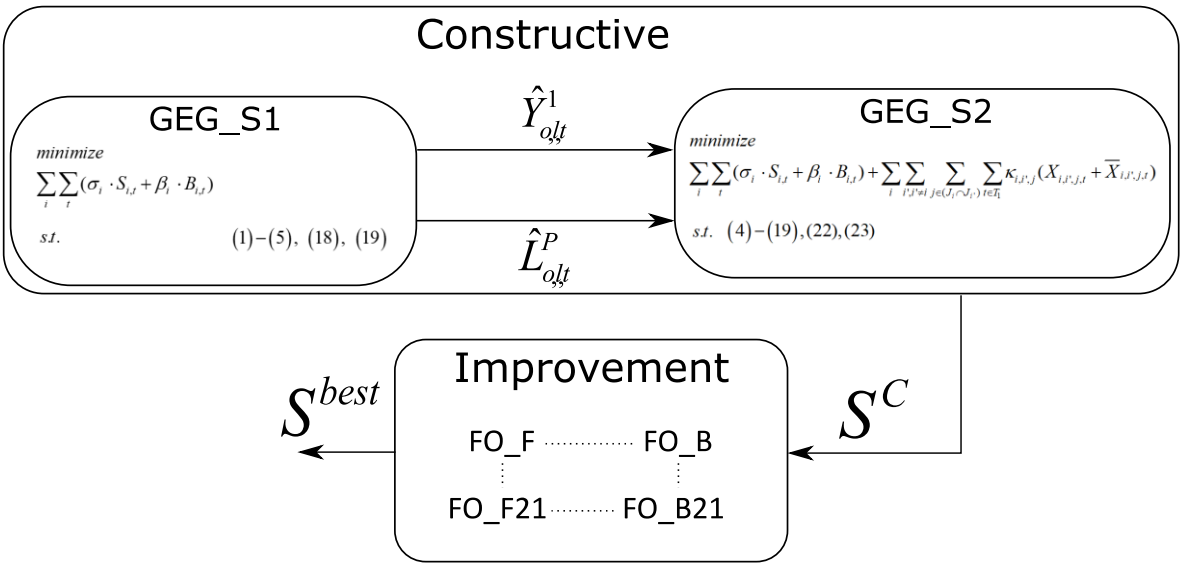

Figure 4.6: Overview of proposed solution strategy

4.4.1 Evaluation of the proposed MILP model

The developed MILP model (GEG) is used to solve numerous test case studies that represent small to medium integrated planning and scheduling problems of brewing facilities. In order to evaluate the quality of the generated production plans, we compare the solutions generated by our model to the ones extracted by the MILP model of Baldo et al. (2014), which to our knowledge is the only model found in literature that can tackle the optimization problem at hand. From now on we will use the name BSAM to refer to that model. A total of 28 case studies have been created, which can be categorized in seven groups based on the number of involved items of the optimization problem (i.e., lines, tanks, liquids, and products). The facility characteristics of each type of case study are displayed in Table 4.1. For each group four alternative case studies are created, that are differentiated in terms of the rest of the production characteristics, e.g., demand mixture (size of orders and due dates), processing times changeover times and cost term coefficients. In order to create realistic case studies, we employ the methodology of Baldo et al. (2014). The specific data for each case study are randomly generated by a set of possible values, that simulate production parameters found in real-life breweries. We now present the interval of values used in the considered case studies. The demand for final products in number of items is in the interval [60, 256710] and the due date of each product is randomly set within the given horizon. Each final product requires an amount

of liquid $r_{l,i}$ that is chosen from the set {1.98, 4.00, 4.80, 5.00, 6.00, 6.00, 6.60, 7.92, 12.00, 17.82, 20.00, 30.00, 50.00}. Processing rates of filling lines range between 0.028 units/second and 9.6 units/second, while the fermentation/maturation process may last from 5 to 21 days. We assume that all filling lines can process every final product. Regarding the changeover times, we randomly equate them to the following values {30, 40, 45, 60, 75, 90, 100, 120, 150, 160, 165, 180, 195, 210, 240, 260, 300, 380, 480, 900}. Furthermore, the unitary inventory cost coefficient (σ_i) of each product over a single time period are defined from the set [0.012,0.45], while the backlog cost coefficient (β_i) is set to be one hundred times the inventory cost coefficient, since the priority is to meet the customer demands prior to the given due date. In order to define changeover cost coefficient, we multiple the respective changeover time with a factor in the range of [10, 100]. Finally, the capacity of the fermentation/maturation tanks is defined based on the specific production characteristics of each problem instance. For more details regarding the generation or realistic case studies refer to Baldo et al. (2014).

Table 4.1: Description of examined case studies

	Tanks	**Lines**	**Liquids**	**Products**
Cases 1.*	3	1	1	5
Cases 2.*	3	1	2	10
Cases 3.*	2	2	2	10
Cases 4.*	4	2	3	15
Cases 5.*	8	2	3	15
Cases 6.*	8	3	4	20
Cases 7.*	10	4	5	25

We employ our model (GEG) to optimally solve the 28 test instances and compare the extracted production plans to the solutions generated by BSAM. For both models a computational limit of half an hour is set. Table 4.2 summarizes the results of this analysis. More specifically, the objective value for each case study, the computational time required, and the optimality gap of the solution is provided for both models. Finally, the

improvement achieved using the suggested MILP model is also reported and was calculated based on the following equation:

$$Improvement = \frac{S_{BSAM} - S_{GEG}}{S_{BSAM}} \cdot 100$$

An improved solution is generated in most cases, proving the superiority of the proposed model, which is especially notable in the larger problem instances (5.*, 6.* and 7.*). There are very few cases in which our model was not able to provide an improved solution, e.g., 4.C and 7.B, however, the solution generated by BSAM in these cases is only marginally better (<5%). In contrast, the utilization of the developed mathematical model, can immensely reduce the production cost. Characteristically, an improvement varying from 10% to 55% is accomplished in many instances. As expected, the larger the problem size the more difficult it is and thus a larger potential for improvement exists. It is interesting to note that even in small-sized cases, where the BSAM solution reaches its best theoretical solution (0% gap), the proposed model can further reduce the objective value. Another important find of this analysis is that the proposed model is much faster than BSAM. In the smaller case studies (1.* - 3.*), GEG achieves similar or better quality solutions using only a fraction of the computational time required by BSAM. For larger problem instances, both models reach the computational limit, except for case 5.C, and in nearly all of them GEG produces a better solution. However, the results also show the limitations of the proposed model. With the exception of small test instances (1.* - 3.*), the solution displays a very large integrality gap, meaning that it is much worse than the theoretically best solution. Thus, a monolithic approach does not suffice, and the development of a sophisticated solution strategy is necessary.

Table 4.2: Comparison between BSAM and GEG models

	BSAM			**GEG**			
Case	**Objective**	**CPU (s)**	**GAP (%)**	**Objective**	**CPU (s)**	**GAP (%)**	**Improvement (%)**
1.A	11177	13.3	0	10067	11.8	0	9.9
1.B	5083	<1	0	5080	<1	0	0.1
1.C	10232	0.15	0	10234	0.15	0	0
1.D	16885	0.5	0	16555	0.2	0	1.9

2.A	247461	1800	20.8	203674	225	0	17.7
2.B	59074	1800	52.5	52274	600	0	11.5
2.C	14874	1800	0.4	14662	224	0	1.4
2.D	1060844	1800	18.3	929332	950	0	12.4
3.A	2825319	1443	0	2336326	3.7	0	17.3
3.B	467805	310	0	467325	104	0	0.1
3.C	80731	444	0	80731	144	0	0
3.D	2657138	484	0	2656117	131	0	0
4.A	2592330	1800	50.5	2122710	1800	31.1	18.1
4.B	1112320	1800	62.2	1066094	1800	53.9	4.2
4.C	24518	1800	70.5	25643	1800	61.4	-4.6
4.D	4628488	1800	83.1	3401497	1800	78.8	26.5
5.A	324848	1800	91.8	200925	1800	80.6	38.1
5.B	32325	1800	37	32491	1800	29.5	-0.5
5.C	45363	24.8	0	46034	6	0	-1.4
5.D	506431	1800	3.5	309656	1800	1.8	38.9
6.A	2546127	1800	65.7	1693735	1800	47.4	33.5
6.B	31386	1800	21.7	28298	1800	8.7	9.8
6.C	18467	1800	57.3	16744	1800	61.4	9.3
6.D	2193641	1800	96.6	1351917	1800	93.88	38.4
7.A	6916373	1800	32.5	5541703	1800	16	19.9
7.B	440177	1800	94.3	451862	1800	93.9	-2.6
7.C	339429	1800	58.3	154366	1800	6.8	54.5
7.D	10446975	1800	100	6858949	1800	91.1	34.3

The combinatorial complexity of an MILP model is mostly affected by the number of binary variables generated. Figure 4.7 illustrates this metric for both GEG and BSAM models. Obviously, the proposed model requires fewer binary variables. In the largest cases, the difference in the number of binary variables between the two models is significantly increased. In particular, up to 30% fewer binary variables are used in the

developed model. Consequently, it is generally faster and can generate better solutions in the same computational time.

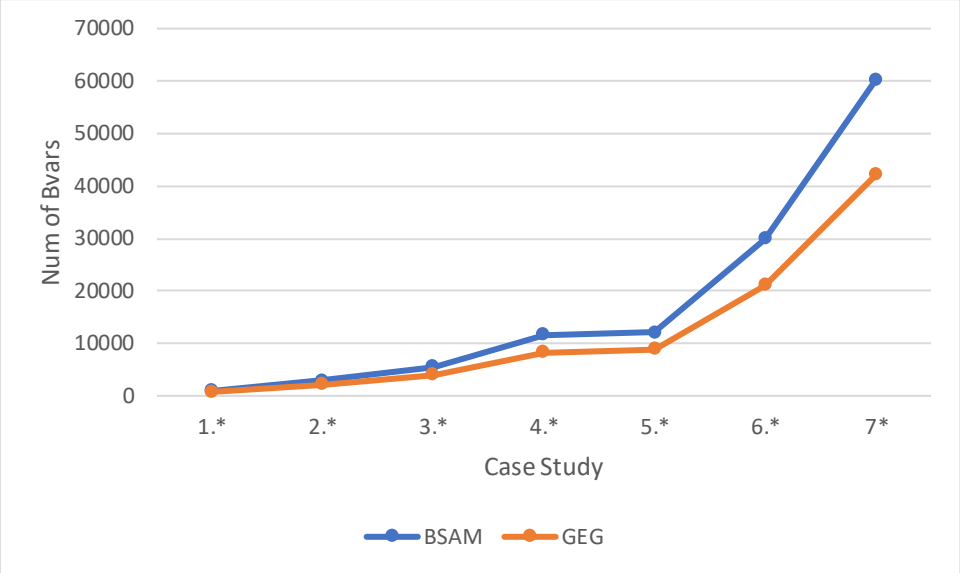

Figure 4.7: Reduction of number of binary variables in the developed model

4.4.2 Evaluation of construction heuristic

The analysis of the previous subsection has uncovered both the advantages and limitations of the proposed model. Therefore, we developed a solution strategy based on that model, in order to address large-scale problems. As described in subsection 4.3.2, this method consists of a constructive and an improvement step. It is crucial to promptly get a good initial solution in the constructive step, in order to improve the performance of the developed solution algorithm. This would not be possible if we just applied the developed model, since it lacks computational efficiency, especially when we deal with real-life situations. Instead, we employed a spatial decomposition approach, that consists of the models GEG_S1 and GEG_S2 that we presented in subsection 4.3.2.1. In this subsection we test how does this approach compare to the monolithic approach of directly applying model GEG. In total we consider seven cases of divergent complexity, which are a subset of the test instances we introduced in the previous subsection. Three approaches are followed in order to solve these cases. In the first two we employ the monolithic approach (GEG) using different computational time limits, 600 seconds, and 1800 seconds accordingly, while in the third we utilize the suggested decomposition

approach with a time limit of 600 seconds. To compare the three approaches, we use the following expression:

$$R = \frac{Found - Best}{Found} \cdot 100$$

The best solution found (Best) is compared to the solution generated by each approach (Found). The better the quality of the solution is, the closer the value of R is to zero. Table 4.3 shows a summary of the results. We found that in small cases there is no difference in the quality of the solution, however the decomposition approach is able to generate faster the optimal production plans. This changes when we are dealing with medium-sized problem instances. Using the same time limit, the solution of the decomposition approach is always better. This effect is stronger in larger cases, were an improvement of up to 50% is reported. The monolithic approach cannot outperform the decomposition method even when we allow three times the computational time. The only exception is case 4.A, where the solution of the decomposition strategy is insignificantly worse but requires only a third of the CPU time. Conclusively, it is shown that the decomposition strategy employed can successfully improve the solutions generated in the constructive step.

Table 4.3: Improvement using construction heuristic

	Monolithic (GEG)				**Decomposition (GEG_S1 + GEG_S2)**	
	limit 600s		**limit 1800s**			
Case	**R (%)**	**CPU (s)**	**R (%)**	**CPU (s)**	**R (%)**	**CPU (s)**
1.A	0	12	0	12	0	9
2.A	0	225	0	225	0	57
3.A	0	4	0	4	0	1
4.A	5.28	600	0	1800	1.79	600
5.A	10.31	600	2.06	1800	0	600
6.A	16	600	8.23	1800	0	600
7.A	52.7	600	41.62	1800	0	600

4.4.3 Evaluation of the developed MILP-based solution strategy

In subsection 4.3.2.2 we introduced four improvement operators (FO_F, FO_B, FO_F21 and FO_B21), based on the fix-and-optimize heuristic, that are used to further enhance the quality of the initial solution. Preliminary tests on numerous case studies were done to evaluate the different operators. For each test we generated an initial solution based on the proposed constructive heuristic and then we applied separately each operator and reported the improvements achieved. The tests showed that the best performer is FO_B, followed by FO_B21, FO_F and finally FO_F21. Based on this information we create two improvement schemes, that differentiate in the order in which the improvement operators are applied. In the first, denominated IMP.A, we employ a greedy approach where the different operators are applied from best to worst (FO_B -> FO_B21-> FO_F -> FO_F21). The second is denominated IMP.B and the reverse order is followed. To evaluate the two improvement schemes, 10 large-scale problem instances are generated. The characteristics of these case studies are as follows. The number of fermentation tanks is in the range [20, 30], while five filling lines comprise the liquid bottling stage. Depending on the considered case, 35 to 40 products, requiring 5 to 7 different liquids, are to be processed. The procedure of generating each problem's parameters is the same as the one described in subsection 4.4.1. For each case study we have used the two alternative improvement schemes and the monolithic approach. Moreover, two time limits (one hour and two hours) were considered for each method. Consequently, six different runs were done for each case study. Note that the improvement schemes are applied to the initial solution provided by the constructive heuristic. Therefore, the available computational time must be shared between the two steps of the proposed solution strategy. Preliminary tests showed that better results were achieved, when a small amount of CPU time is allocated to the generation of the initial solution. Therefore, a time limit of 450 seconds is set for the constructive step. The rest of the available CPU time (3150 or 6750 seconds depending on the test instance) is used in the iterative improvement step. In Table 4.4 a summary of the results is portrayed. The relative quality of each solution is reported using the R value described in the previous subsection. The solutions generated by any of the two proposed methods is much better than the solutions obtained by the MILP model, even when we use twice the computational time. It should be underlined that on average the initial solutions provided

by the constructive step are better than the ones obtained by the model using any time limit. Note that the constructive heuristic runs only for a very small fraction of time compared to GEG. On average IMP.B delivered the best solutions, however in some case studies the application of IMP.A resulted to production plans of better quality. More clear conclusions can be drawn when a time limit of two hours is employed. Here IMP.B is clearly the better approach, since it provides the best solution in nearly all case studies. Conclusively, both solution strategies seem promising, since they outperform the direct application of CPLEX on the MILP model (GEG), on every large-scale problem. Thus, the results indicate that the proposed methods can successfully address real-life industrial problems. We note that as the runtime limits increase, the performance of both methods is improved. Finally, the order of applying the improvement operators affects the performance of the improvement step. In particular, better solutions are extracted in most cases, when we apply the operators from worst to best.

Table 4.4: Comparison between the MILP model and the proposed solution strategy approaches for large-scale case studies

Case	Limit (3600s)				Limit (7200s)		
	GEG (%)	**Constructive (%)**	**IMP.A (%)**	**IMP.B (%)**	**GEG (%)**	**IMP.A (%)**	**IMP.B (%)**
L1	85.4	68.3	22	29.3	49.7	19.3	0
L2	39.3	18.6	7.4	7.4	39.3	0	1.8
L3	55.7	27.7	12.2	10.5	38.2	11.3	0
L4	52.5	33.3	32	4.9	49.6	17.8	0
L5	18.4	3.5	0.4	0.4	15.8	0	0.3
L6	68	62.7	47.4	19.7	43.7	27.9	0
L7	73.7	40.9	1.6	23.1	50.9	0	2
L8	55.7	29.2	4.3	3.2	9.5	2.3	0
L9	67.1	19.2	2.1	3	54.8	0.7	0
L10	72.7	85.7	41	2.3	40.5	25.9	0
Average	58.85	38.91	17.04	10.38	39.2	10.52	0.41

4.4.4 Industrial application

The applicability of the proposed solution strategy in real-life industrial problems is tested in this subsection. In particular, a case study provided by a brewery located in Northern Greece is considered. The facility under consideration consists of 31 fermentation/maturation tanks and two filling lines. The tanks are divided in tree types, small, medium, and large, depending on their capacity. Regarding the filling lines, the first one can process all products that use aluminium cans or glass bottles, while the second only produces final items that use kegs. A total of nine products that require two types of liquids are produced in the facility. However, multiple orders for each final product that usually have different amounts and due dates must be satisfied in the considered horizon, thus increasing the complexity of the problem. The planning horizon is set to six weeks, while the optimal scheduling decisions are required over a weekly horizon. The plant operates throughout the clock, so there is a 24/7 availability for all processing units. Due to confidentiality reasons, we cannot share any processing data and therefore we also cannot compare the optimized production plans with the ones generated by the production engineers. In the considered problem instance, a total of 36 orders must be met. The proposed solution method is employed to generate optimal production plans that minimize the total production costs (inventory, backlog, and changeover) of the facility. In the improvement step, we apply the operators from worst to best (IMP.B approach), due to its superior performance. The chosen computational limit is set to 2 hours.

Figure 4.8 illustrates the Gantt chart of the optimized solution for each fermentation/maturation tank. Each block signifies the fermentation/maturation process of a liquid that takes places in a tank. Note that by the end of the planning horizon no fermentation process occurs. This is justified by the limited considered horizon. The fermentation/maturation process requires a total of 21 days, consequently, no liquid can be prepared in the available time, therefore no additional process can start.

In Figure 4.9 the Gantt chart of the filling lines is portrayed. Each coloured block denotes that a filling process for a specific order is taking place. At a first look one would say that there is no need for incorporating this stage and that the production bottleneck is the fermentation/maturation stage. It is true that the results, underline an overdesign issue of the filling lines in the examined facility. However, they must be included in the

optimization problem for two reasons. Firstly, the changeovers that take place in the liquid filling stage must be incorporated since they induce significant costs either due to the loss of production time or the due to the resources required for cleaning operations e.g., water and manpower. Moreover, there must always be available filling lines for the tanks to empty the ready liquid and be refilled to initiate the next fermentation process. It must be ensured that the capacity of the filling lines is never violated, otherwise no feasible production plan can be achieved for the fermentation tanks.

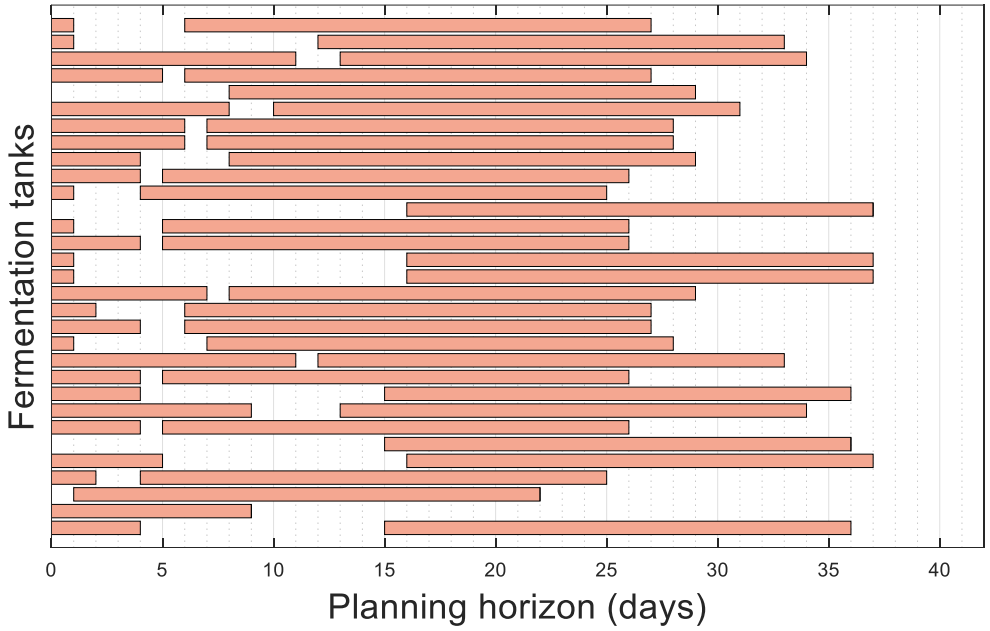

Figure 4.8: Gantt chart of the fermentation/maturation tanks

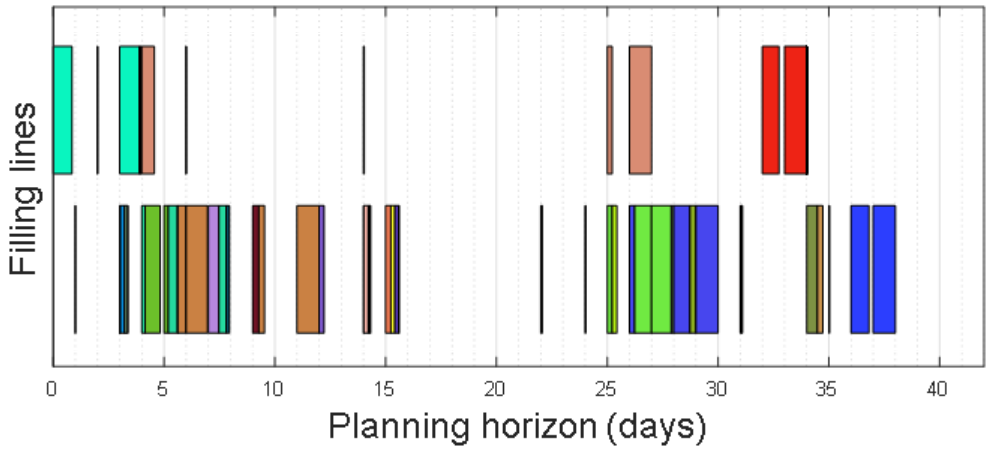

Figure 4.9: Gantt chart of the filling lines

Finally, Figure 4.10 depicts the amount of stored ready liquid in a representative sample of the fermentation tanks. It can be observed that the tank capacity limitations are respected throughout the planning horizon.

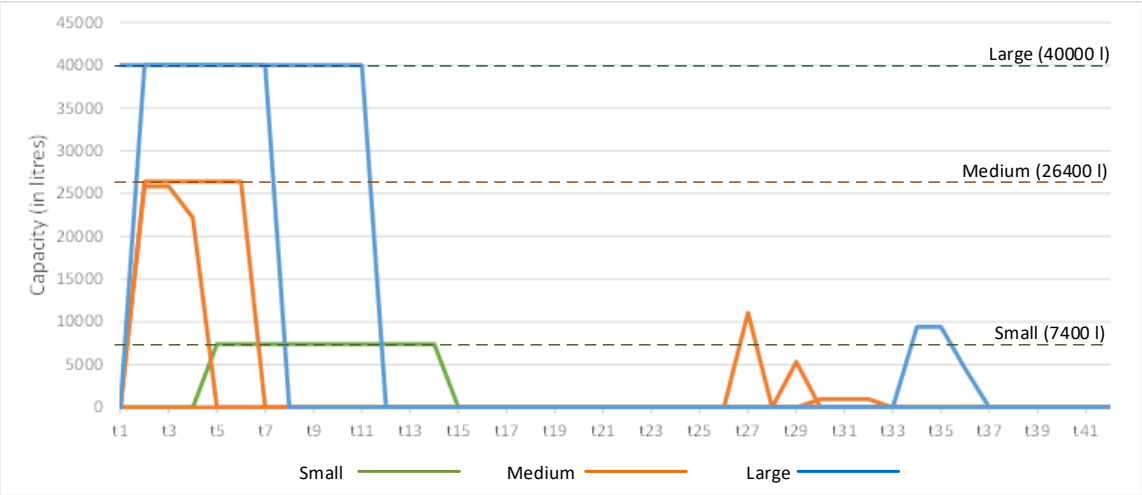

Figure 4.10: Amount of liquid stored in a representative sample of the fermentation tanks

4.5 Conclusions

In this chapter a new MILP-based solution strategy is proposed for the optimal production planning and scheduling problem of breweries. The overall production procedure consists of a batch (liquid preparation) and a continuous (liquid bottling) processing stage. Numerous parallel non-identical units such as fermentation/tanks and filling lines are available in each stage, while a large number of orders must be satisfied as close as possible to their specified due dates. A salient characteristic of this process are the very long lead times originating from the large processing time required for the fermentation/maturation process. Therefore, a long planning horizon must be considered, resulting to a very difficult optimization problem. In order to efficiently address the problem, a new MILP model is developed based on the immediate precedence framework and relying on a mixed discrete-continuous time representation. A comprehensive analysis demonstrated that the developed model performs superior to the only other suitable model currently available in literature. However, the direct application of the MILP model is limited to small problem instances. Therefore, an optimization-based solution strategy is introduced, in order to tackle large-scale case studies that simulate the industrial reality. The suggested algorithm consists of a

constructive step, that utilizes a spatial decomposition heuristic to propose an initial good solution and an improvement step, where four operators based on the fix-and-optimize heuristic are applied to achieve high quality solutions. The proposed solutions strategy is successfully applied in a real-life industrial problem of a Greek brewery. Optimized production plans that minimize the total production costs are generated in low CPU times. The suggested optimization framework can be the core part of a computer-aided tool, that will facilitate the decision-making process in any brewing facility of arbitrary complexity. As a result, near-optimal production plans can be promptly generated, thus leading to significant economic benefits and to the overall improvement of the industry's competitive advantage.

Nomenclature

Indices

$i, i' \in I$	products to be processed within the planning horizon
$l, l' \in L$	liquids required for the final products
$o \in O$	fermentation/maturation tanks
$j \in J$	filling lines
$t, t' \in T$	set of time periods for the whole planning horizon

Sets

T_1	subset of time periods that comprise the first part of the planning horizon
T_2	subset of time periods that comprise the second part of the planning horizon
I_j	mapping set defining filling lines *j* that can process product *i*
J_i	mapping set defining products *i* that can be processed by filling line *j*

I_l	mapping set defining products *i* that are made of liquid *l*

Parameters

λ_l	fermentation/maturation time required for liquid *l*
χ_o	maximum capacity of fermentation/maturation tank *o*
$\pi_{i,l}$	amount of liquid *l* required for each unit of product *i*
$\rho_{i,j}$	processing rate of product *i* in filling line *j*
$\gamma_{i,i',j}$	necessary changeover time between products *i* and *i'* in filling line *j*
$\zeta_{i,t}$	demand of product *i* in time period *t*
σ_i	inventory cost coefficient
β_i	backlog cost coefficient
$\kappa_{i,i',j}$	changeover cost coefficient
ω	available processing time in each time period
M	big-M parameter used for the lot-sizing constraints of the liquid preparation stage

Variables

Binary

Stage 1	
$Y^1_{o,l,t}$	=1 when liquid *l* gets ready in tank *o* in time period *t*

Stage 2	
$Y^2_{i,j,t}$	=1 when product *i* is processed in filling line *j* in time period *t*
$V_{j,t}$	=1 when filling line *j* is utilized

$W^{F}_{i,j,t}$	=1 when product *i* is processed first in filling line *j* in time period *t*
$W^{L}_{i,j,t}$	=1 when product *i* is processed last in filling line *j* in time period *t`*
$X_{i,i',j,t}$	=1 when product *i* is processed right before product *i'* in line *j* and time period *t*
$\bar{X}_{i,i',j,t}$	=1 when product *i* is the last to be processed in line *j* period *t* and product *i'* is the first to be processed in the same line in time period *t+1*

Continuous

Stage 1	
$L^{P}_{o,l,t}$	amount of liquid *l* that gets ready in tank *o* in time period *t*
$L^{S}_{o,l,t}$	amount of stored liquid *l* that gets ready in tank *o* in time period *t*

Stage 1+2	
$L^{T}_{o,j,i,t}$	amount of liquid *l* being transferred from tank *o* to line *j* in time period *t*

Stage 2	
$Q_{o,j,i,t}$	number of items *i* that use liquid from tank *o* and are processed in line *j* in time period *t*
$C_{i,j,t}$	completion time of the filling process for product *i* in filling line *j* and time period *t*
$U_{j,t}$	time within period *t* used for a changeover operation that is completed in the next period in filling line *j*
$\bar{U}_{j,t}$	time within period *t* used for a changeover operation that started in the previous period in filling line *j*
$S_{i,t}$	inventory level of product *i* in time period *t*
$B_{i,t}$	backlog level of product *i* in time period *t*

Chapter 5

Optimal Planning of the COVID-19 Vaccine Supply Chain

5.1 Introduction

The focus of this thesis so far is on the optimization of production planning and scheduling on a large variety of industrial problems. This chapter addresses an emerging supply chain optimization problem related to the COVID pandemic. Production planning and scheduling constitute the most important decision-making procedure in manufacturing, which is an integral part and considered as a critical phase of any supply chain. Furthermore, the mathematical frameworks for production planning and supply chain optimization illustrate significant similarities. So, in this chapter, we broaden the field of our research by extending the knowledge acquired in chapters 2 to 4 to study a new and challenging supply chain planning problem emerging from the COVID-19 vaccination.

More specifically, this chapter is considered with the optimal short-term planning of the COVID-19 supply chain by proposing a novel MILP-based framework. Tactical and operational decisions regarding the inventory levels in the central hubs and the vaccination centres, the flows between the various locations of the distribution network, the fleet requirements, the scheduling of citizens' vaccinations, as well as, staffing of the vaccination centres are considered. The developed model cleverly addresses key issues of the COVID-19 supply chain, like storage and supply limitations, multiple cold storage technologies, demanding vaccination targets, transportation lead-times and vaccine perishability. Goal of the optimization is the minimization of cost including, storage costs, fleet rental, fuel consumption, drivers' wages, cost of wasted doses and possible needs in additional healthcare personnel. An optimization-based solution strategy is introduced to address large-scale realistic case studies and is successfully applied to a case simulating the Greek COVID-19 supply chain. Furthermore, a rolling-horizon technique is

incorporated to replan the supply chain, in case of demand fluctuations originating from citizens that reschedule their vaccination appointment at the last minute or do not arrive on a scheduled appointment.

5.2 Problem Statement

The problem addressed in this chapter considers the optimal short-term planning of the COVID-19 VSC, as well as the optimal planning of appointments in the vaccination centres, in order to minimize the total costs. Figure 5.1 illustrates a generic representation of the underlying network. The supply chain consists of three echelons: the manufacturing plants with a known maximum production capacity, the hubs, where the vaccine vials are stored and transferred to the vaccination centres, where the citizens are vaccinated. The product (vaccines) flow is unidirectional, from the manufacturers to the hubs and finally to the vaccination centres. Reverse flows from the vaccination centres to the hubs are not allowed, while intralayer flows between the hubs or the vaccination centres are not considered. Finally, the vaccines are used in the vaccination program of the population. Planning of the appointments is considered simultaneously with planning the distribution of the COVID-19 vaccines. The capacity of each vaccination centre depends on the number of active vaccination lines. Each vaccination line operates in two 6-hour shifts from Monday to Saturday, and employs two health workers, one nurse and one doctor. The vaccination centres are closed on Sundays. To properly consider the low shelf-life of sensitive vaccines (5 days), a 14-day horizon is considered. The described problem is implemented in terms of an MILP model that relies on a daily discretization of the bi-weekly time horizon. Within the given horizon a specific number of completed appointments must be satisfied. The model distributes this number throughout the available time periods. As a result, optimal decisions regarding the daily appointments at each centre are generated, which impose the needs in healthcare personnel in each centre and time period.

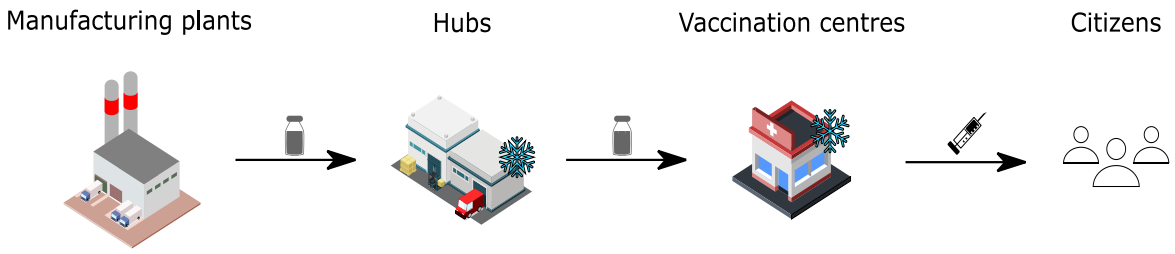

Figure 5.1: COVID-19 Vaccine Supply Chain Representation

A total of four vaccines simulating the different characteristics of the main vaccines currently used in Europe and the USA are considered in the overall vaccination plan and supply chain. In particular, the vaccines of Astrazeneca (A), Johnson& Johnson (J), Moderna (M) and Pfizer (P) are considered. Extension to more types of vaccines is straightforward. The hubs are equipped with all necessary cold storage technologies for the long-term storage of the vaccines. More specifically, deep freezers (-70^{o}C) are required for Pfizer and regular freezers (-20^{o}C) for Moderna vaccines, while simple refrigeration suffices for the non-mRNA alternatives (A and J). In contrast, the vaccination centres are only equipped with regular refrigerators. This reinforces the need for the proper organization of the supply chain, since mRNA vaccines, especially the Pfizer vaccine, cannot be maintained long-term in such conditions. Otherwise, a huge number of valuable doses may be spoiled, thus hindering the prompt vaccination of the citizens. Therefore, all perishability considerations are included in the proposed MILP model.

A homogeneous fleet of trucks is employed to transport the vaccines from the hubs to the vaccination centres. The trucks are equipped with the necessary technology to maintain low temperatures during transportation and ensure that the cold chain remains uninterrupted. Vehicle routing is not considered in this study. It is assumed that in each time period a truck can visit a single vaccination centre and must return to the hub from which it started. A specific time is necessary for the transportation of vaccines between the echelons of the supply chain. The lead time could be easily incorporated in case a finer discrete time grid, e.g., hourly, was utilized, however that would lead to a huge MILP model, thus worsening its computational efficiency. To bypass this obstacle, it is assumed that the vaccines must remain for a period in every location of the supply chain. For example, if a quantity of vaccines is transferred in period t from the manufacturing plant

to a hub, then this quantity is only available to be transferred to the vaccination centres after period *t+1*. Similarly, if a quantity arrives in a vaccination centre in period *t+1*, this will only be available to be used in an appointment after period *t+2*.

An important issue in VSCs is related with the wasted doses. This is especially relevant for perishable products like the mRNA COVID-19 vaccines. The World Health Organization (WHO) categorizes the wasted doses into closed vial wastage, which is caused by inefficiencies in the supply chain and open vial wastage, which is further divided into avoidable and unavoidable open vial wastage (World Health Organization 2019). The first is attributed to immunization workers' and include errors in patient's reactions, suspected contamination, reconstitution, and excess heat. The latter refers to the discarded doses from multidose vials. Notice that each vial contains multiple doses, once a vial is firstly opened, all doses must be used within the same day, otherwise all remaining doses must be discarded. Closed vial wastage and avoidable vial wastage are included in the model based on the wastage ratios recommended by WHO. The minimization of the unavoidable open vial wastage is included in the objective function of the proposed model.

The problem under study can be formally stated as follows. Given:

- A known planning horizon H divided into a set of time periods $t \in T$.
- A set of locations $i \in I$ with an initial storage of vaccine v $\alpha_{i,v}$, a wastage ratio β_i and a desired safety stock $\varepsilon_{i,v}$. Furthermore, the distance between all locations is given $\mu_{i,j}$, as well as a minimum and maximum flow of vaccine vials between each pair of locations, $\rho_{i,j}^{min}$ and $\rho_{i,j}^{max}$ accordingly.
- A set of manufacturing plants $f \in F$.
- A set of hubs $h \in H$ that can handle a maximum supply of vaccine v $\pi_{h,v}^{max}$
- A set of vaccination centres $vc \in VC$, with a maximum storage capacity θ_{vc}, a vaccination appointment goal within the horizon ζ_{vc} and a number of readily available healthcare workers ι_{vc}.
- A set of vaccines $v \in V$ to be distributed and a subset of vaccine types $sl \in SL_v$, that are characterised by a limited shelf-life. Also given are the doses per vial of vaccine v δ_v, the shelf-life λ_v and the cost of each dose of vaccine type ξ_v.

- A set of cold storage technologies $c \in C$ to safely store the different vaccine types with a given operating cost ψ_c. Moreover, the storage capacity of each technology in the hubs ($\gamma_{h,c}$) is provided.
- The multidimensional set $IJ_{i,j}$ that denotes the connectivity between the various locations of the supply chain.
- The multidimensional set $CV_{c,v}$ that defines the cold storage technology required for every vaccine type.
- The multidimensional set $FV_{f,v}$ which characterises the vaccines that are produced by each manufacturing plant.

Determine:

- The amount of vaccine vials that is supplied by the manufacturers at each period $P_{f,v,t}$.
- The transferred amounts of vials of each vaccine between the locations of the supply chain in each period $X_{i,j,v,t}$.
- The inventory profile in all locations and every period $S_{i,v,t}$.
- The daily vaccination appointments in each location and period $DA_{vc,t}$.
- The vials of each vaccine type that are opened in each period $VU_{vc,v,t}$ and the doses that are used in the vaccination plan $DU_{vc,v,t}$.
- The doses that are wasted due to open vials that are not fully exploited within a period $WD_{vc,v,t}$ or due to expiration $WE_{i,t}$.
- The number of healthcare workers required to realize the vaccination plan $HW_{i,t}$.
- The fleet size of trucks necessary to distribute the vaccines from the hubs to the vaccination centres NT.

, so that the total cost of the supply chain consisting of i) the storage costs, ii) the distribution costs (fuel consumption and drivers' wages), iii) the compensation for any additional healthcare personnel, iv) the wasted doses and v) the rental cost of the fleet, is minimized.

5.3 Mathematical framework

In this chapter the MILP-based mathematical frameworks that have been developed to deal with the optimization problem of planning the COVID-19 VSC are presented. A novel MILP model is presented that can generate optimal decisions for small to medium problems. Specific characteristics of the COVID-19 VSC such as the limited shelf life of the vaccines, are cleverly incorporated. Despite the efficiency of the proposed models, the combinatorial complexity of large nation-wide problems exceeds the computational capabilities of any known solver, e.g., CPLEX, therefore, a solution strategy based on the proposed MILP model is also investigated.

5.3.1 MILP model

The developed model utilizes a discrete time grid to efficiently encapsulate the inventory balances in the various locations of the supply chain. The constraints related to the material balances, inventory capacities and vaccine flows are inspired by the model proposed in Carvalho, Ribeiro, and Barbosa-Povoa (2019), which studies the long-term design and planning problem of a VSC. In contrast, this paper considers the short-term planning of the VSC, while taking into account the undergone vaccination plan in each vaccination centre. Therefore, the studied two-week planning horizon is discretized into 14 daily time periods. Additional to the material balance, inventory capacity and flow limitation constraints, the proposed model introduces efficient constraints for the incorporation of lead time, shelf-life limitations, and the vaccination plan. All constraints of the model are described in detail below. To facilitate the presentation of the model, lowercase Latin letter are used for indices, uppercase Latin letters for variables and lowercase Greek letters for parameters.

Supply constraints

The supply limitations provided by the manufacturer are expressed by the following constraints. More specifically, constraint (5.1) ensures that the vials of vaccine v supplied by the corresponding manufacturer f ($P_{f,v,t}$) throughout the considered planning horizon are limited by the upper bound of production ($\pi_{h,v}^{max}$). Furthermore, it

is assumed that each manufacturer *f* can supply each hub *h* at most once per week, as imposed by constraint (5.2).

$$\sum_{f \in FV} \sum_{t} P_{f,v,t} \leq \pi_{h,v}^{max} \qquad \forall h,v \qquad (5.1)$$

$$\sum_{t \in TW} Y_{f,h,t} \leq 1 \qquad \forall f,h,w \qquad (5.2)$$

Material balances

Constraints (5.3) - (5.7) encapsulate the material balances around each location of the supply chain. Firstly, constraints (5.3) guarantee that the amount of a vaccine *v* transferred from a factory *f* to all hubs *h* ($X_{f,h,v,t}$) equals the total amount supplied by the factory in time period *t*. The next two constrains set the material balances around the hubs. Constraints (5.4) state that the inventory at the end of the first time period equals the initial inventory of the hub ($\alpha_{h,v}$) plus the amount transferred from the factories, minus the amount that has been sent to the vaccination centres ($X_{h,vc,v,t}$) and the amount of vials lost ($LS_{h,v,t}$). For all next time periods, the constraints remain the same, but instead of using the initial inventory, the inventory of the previous period is used. Similarly, constraints (5.6) and (5.7) monitor the material balances around the vaccination centres. Finally, constraint (5.8) calculates the vials of vaccine *v* lost in each location *i* and time period *t*, as the factor of the stored vials and the known wastage ratio of the location (ρ_i).

$$\sum_{h} X_{f,h,v,t} = P_{f,v,t} \qquad \forall f \in fv, v, t \qquad (5.3)$$

$$S_{h,v,t} = \alpha_{h,v} + \sum_{f} X_{f,h,v,t} - \sum_{vc \in HVC} X_{h,vc,v,t} - LS_{h,v,t} \qquad \forall h,v,t = 1 \qquad (5.4)$$

$$S_{h,v,t} = S_{h,v,t-1} + \sum_{f \in FV} X_{f,h,v,t} - \sum_{vc \in HVC} X_{h,vc,v,t} - LS_{h,v,t} \qquad \forall h,v,t > 1 \qquad (5.5)$$

$$S_{vc,v,t} = a_{vc,v} + \sum_{h \in HVC} X_{h,vc,v,t} - VU_{vc,v,t} - LS_{vc,v,t} \qquad \forall vc,v,t = 1 \qquad (5.6)$$

$$S_{vc,v,t} = S_{vc,v,t-1} + \sum_{h \in HVC} X_{h,vc,v,t} - VU_{vc,v,t} - LS_{vc,v,t} \qquad \forall vc, v, t > 1 \qquad (5.7)$$

$$LS_{i,v,t} = S_{i,v,t} \cdot \rho_i \qquad \forall i, v, t \qquad (5.8)$$

Inventory constraints

The following constraints are concerned with the inventory considerations of the supply chain. Constraint (5.9) imposes a minimum safety stock at the end of the planning horizon ($\varepsilon_{i,v}$), which is required to ensure the future availability of vaccines in the hubs and the vaccination centres. The storage capacities of the various technologies in the hubs ($\gamma_{c,h}$) and the vaccination centres (θ_{vc}) are respected by constraints (5.10) and (5.11) accordingly.

$$\sum_{v} S_{i,v,t} \geq \sum_{v} \varepsilon_{i,v} \qquad \forall i \in (vc_i \cup h_i), t = |T| \qquad (5.9)$$

$$\sum_{v \in CV} S_{h,v,t} \leq \gamma_{c,h} \qquad \forall h, c, t \qquad (5.10)$$

$$\sum_{v} S_{vc,v,t} \leq \theta_{vc} \qquad \forall vc, t \qquad (5.11)$$

Flow limitations

A minimum ($\rho_{i,j}^{min}$) and a maximum flow ($\rho_{i,j}^{max}$) is allowed during the transportation of vaccine vials between two locations. These bounds are set for the vial flows between factories and hubs and between hubs and vaccination centres by constraints (5.12) and (5.13) accordingly. Notice that when a connection is not realized in time period t ($Y_{i,j,t} = 0$), the associated transferred quantities ($X_{i,j,v,t}$) are pushed to zero.

$$\rho_{f,h}^{min} \cdot Y_{h,vc,t} \leq \sum_{v \in FV} X_{f,h,v,t} \leq \rho_{f,h}^{max} \cdot Y_{h,vc,t} \qquad \forall f, h, t \qquad (5.12)$$

$$\rho_{h,vc}^{min} \cdot Y_{h,vc,t} \leq \sum_{v} X_{h,vc,v,t} \leq \rho_{h,vc}^{max} \cdot Y_{h,vc,t} \qquad \forall h \in HVC, vc, t \tag{5.13}$$

Transportation time considerations

An important characteristic of the studied supply chain that should be considered, concerns the required transportation time between the supply chain nodes. Theoretically, within the same day a vial could be transferred from the manufacturers to the hubs and then the vaccination centres to be used. However, this would require a finer discretization of time, that would lead to large and inefficient models. Therefore, to ensure the feasibility of the proposed logistics operations using a daily discretization, it is assumed that a vial that is transferred from a factory to a hub in time period *t*, can only be further transferred to a vaccination centre after the next time period (*t+1*). The same holds for the hubs to vaccination centres connections. In particular, a vial that is transferred from a hub to a vaccination centre in time period t can only be used for the vaccination plan of a vaccination centre after time period *t+1*. This assumption is introduced to the model through constraints (5.14) and (5.15). Figure 5.2 illustrates the role of the constraint for the vaccination centres. More specifically, the vials of vaccine *v* used in the vaccination plan in a centre for all time periods $t' \leq t$, must be less than or equal to the initial inventory of vials plus the vials that arrived from the hubs in all time periods $t'' \leq t-1$, minus the vials lost in the same time periods. A similar logic is followed for the hubs.

$$\sum_{vc} \sum_{t' \leq t} X_{h,vc,v,t'} \leq a_{h,v} + \sum_{f \in FV} \sum_{t'' \leq t-1} X_{f,h,v,t''} - \sum_{t'' \leq t-1} LS_{h,v,t''} \qquad \forall h, v, t \tag{5.14}$$

$$\sum_{t' \leq t} VU_{vc,v,t'} \leq a_{vc,v} + \sum_{h} \sum_{t'' \leq t-1} X_{h,vc,v,t''} - \sum_{t'' \leq t-1} LS_{vc,v,t''} \qquad \forall h, v, t \tag{5.15}$$

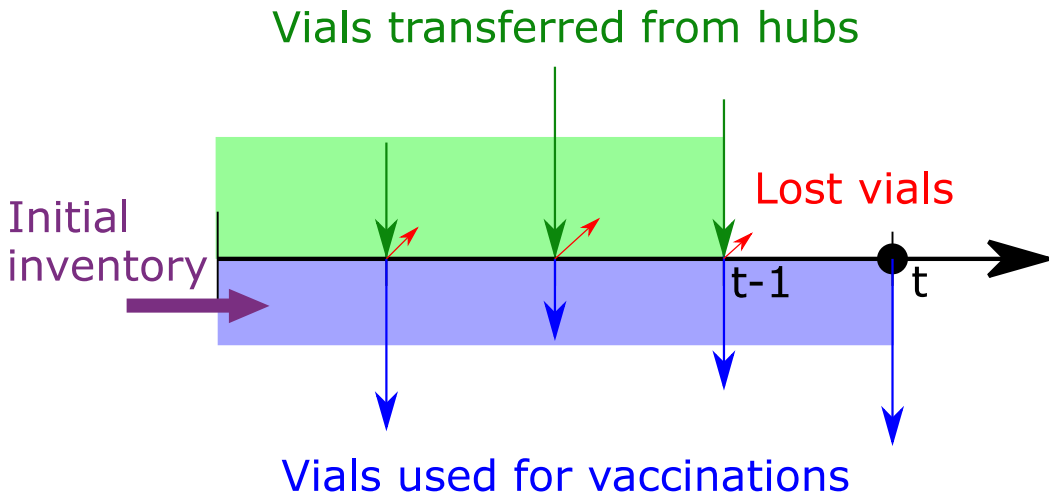

Figure 5.2: Description of transportation time constraints

Shelf-life of vaccines

To incorporate shelf-life issues in the model, a new variable $L_{vc,v,t,t'}$ is introduced, which defines the quantity of vials of vaccines v used in centre vc in time period t' that have been transferred to the centre in time period t. Constraints (5.16) state that the vials transferred to a vaccination centre in time period t are either used in the vaccination plan of the next time periods within the shelf-life of the specific vaccine (λ_{sl}) or are spoiled $WE_{vc,t}$. In case the time periods after t exceed the considered horizon, constraints (5.17) are activated, to ensure that the vials used do not surpass the vials transferred. Another continuous variable is included to model the quantity of vials that existed in the initial inventory and were used in the vaccination plan of time period t ($SU_{vc,v,t}$). The next constraints connect the total quantity of vials used in the vaccination plan of period t ($VU_{vc,v,t}$), with the newly introduced variables. Figure 5.3 depicts the connection between variables $L_{vc,v,t,t'}$, $VU_{vc,v,t}$ and $X_{h,vc,v,t}$. In the illustrated example, the vials used in time period *t5* originate from quantities transferred in the vaccination centre in time periods *t1* and *t3*. Finally, constraints (5.20) calculate the number of vials that belong in the initial inventory and are spoiled ($WE^{I}_{vc,t}$). Notice that the constraints below are only generated for the vaccines with shelf-life issues ($v \in sl$).

$$\sum_{t'\geq t+1}^{t+\lambda_{sl}} L_{vc,v,t,t'} + WE_{vc,t} = \sum_{h\in HVC} X_{h,vc,v,t} \qquad \forall vc, v \in SL, t \leq (|T| - \lambda_{sl}) \qquad (5.16)$$

$$\sum_{t'\geq t+1} L_{vc,v,t,t'} \leq \sum_{h\in HVC} X_{h,vc,v,t} \qquad \forall vc, v \in SL, t > (|T| - \lambda_{sl}) \qquad (5.17)$$

$$VU_{vc,sl,t'} = SU_{vc,sl,t'} + \sum_{t\leq t'-1} L_{vc,sl,t,t'} \qquad \forall vc, sl, t' \leq \lambda_{sl} \qquad (5.18)$$

$$VU_{vc,sl,t'} = \sum_{t\geq t'-\lambda_{sl}}^{t'-1} L_{vc,sl,t,t'} \qquad \forall vc, sl, t' > \lambda_{sl} \qquad (5.19)$$

$$\sum_{t\leq \lambda_{sl}} SU_{vc,sl,t} + WE^{I}_{vc} = \alpha_{vc,sl} \qquad \forall vc, sl \qquad (5.20)$$

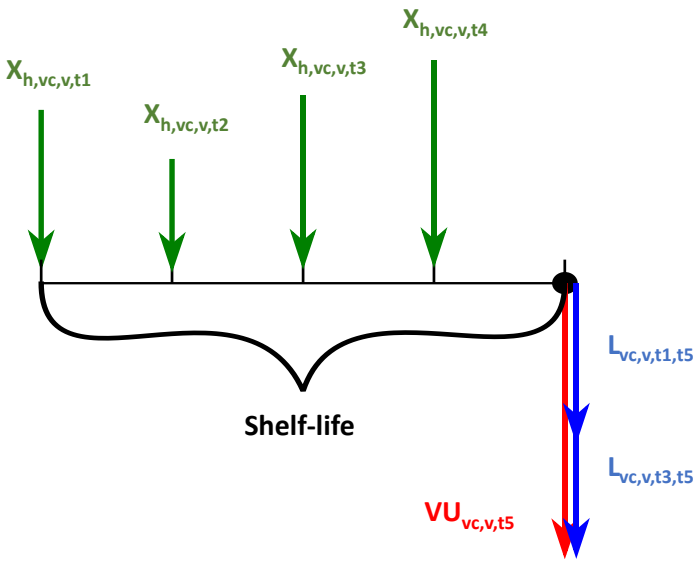

Figure 5.3: Relationship between variables $L_{vc,v,t}$ and $VU_{vc,v,t}$

Vaccination plan constraints

The daily vaccination appointments in centre vc and period t ($DA_{vc,t}$) are calculated as the summation of the doses of all vaccines v used in the respective centre ($DU_{vc,v,t}$), as given in constraints (5.21). Constraints (5.22) define the number of vaccine

doses as the product of the vials used and the number of doses in each vial. Attaining the vaccination target within the planning horizon is ensured by constraints (5.23).

$$\sum_{v} DU_{vc,v,t} = DA_{vc,t} \qquad \forall vc,t \qquad (5.21)$$

$$VU_{vc,v,t} \cdot \delta_v = DU_{vc,v,t} \qquad \forall vc,v,t \qquad (5.22)$$

$$\sum_{t} DA_{vc,t} = \zeta_{vc} \qquad \forall vc \qquad (5.23)$$

Healthcare workers and fleet constraints

Constraints (5.24) and (5.25) define the requirements in healthcare personnel for the vaccination plan. The number of daily appointments in a vaccination centre is dependent on the number of active vaccination lines in the centre ($HW_{vc,t}$). Each vaccination line consists of two health workers that can complete η vaccinations per time period. Every vaccination centre has a base number of vaccination lines available (ι_{vc}). The additional number of lines required for the optimal vaccination plan is portrayed by variable ($AH_{vc,t}$). The fleet size required for distributing the vaccines from the hubs to the vaccination centres (NT) is calculated by constraints (5.26).

$$DA_{vc,t} \leq \eta \cdot HW_{vc,t} \qquad \forall vc,t \qquad (5.24)$$

$$AH_{vc,t} \geq HW_{vc,t} - \iota_{vc} \qquad \forall vc,t \qquad (5.25)$$

$$\sum_{h} \sum_{vc \in HVC} Y_{h,vc,t} \leq NT \qquad \forall vc,t \qquad (5.26)$$

Wasted doses constraints

The vaccine doses wasted due to open vials that are not completely used within a period are included in the model by constraints (5.28). An integer variable is introduced to calculate the actual number of vials of vaccine *v* opened in vaccination centre *vc* and time period *t* ($VU^{I}_{vc,v,t}$), as shown in constraints (5.27). Finally, the doses available in the

opened vials are subtracted by the actual doses used in the vaccination plan to calculate the number of wasted doses ($WD_{vc,v,t}$).

$$VU^{I}_{vc,v,t} \geq VU_{vc,v,t} \qquad \forall vc,v,t \qquad (5.27)$$

$$WD_{vc,v,t} = (VU^{I}_{vc,v,t} - VU_{vc,v,t}) \cdot \delta_{v} \qquad \forall vc,v,t \qquad (5.28)$$

An economic objective is considered to minimize the total cost of the vaccine supply chain (5.29). The total cost terms include the following in the respective order:

- Storage operating costs in the hubs are given by the number of vials stored in each hub ($S_{h,v,t}$) multiplied by the unitary storage costs for each storage technology (κ_c).
- Storage operating costs in the vaccination centres are given by the multiplication of the vials stored in each vaccination centre and the unitary storage costs. Only the refrigeration storage technology is employed in the vaccination centres.
- The transportation costs consisting of the costs for fuel and the cost of the drivers. These costs are included in the objective function, only when a connection between a hub and a vaccination centre exists in period t ($Y_{h,vc,t} = 1$). The fuel consumption cost is provided by multiplying the distance travelled ($2 \cdot \mu_{h,vc}$), the cost of fuel (κ) and the average fuel consumption per 100km (φ). Notice that since the trucks need to return to the corresponding hubs in each period, the distance ($\mu_{h,vc}$) must be multiplied by two. Regarding the drivers' cost, it is calculated based on the total hours a driver is employed, which is given by dividing the distance travelled and the average speed of a truck (τ), and the hourly wage of a single driver (o).
- Cost of wasted doses due to unproper planning in the vaccination centres is given by three terms. In the first the wasted doses of open vials which are not fully used in the daily vaccination program ($WD_{vc,v,t}$) are multiplied with the cost of a single vaccine dose (ξ_v). The next two terms consider the vials that were initially stored and the vials that were transferred within the studied horizon which have expired (WE^{I}_{sl} and WE_{sl} accordingly). To calculate these terms, the associated values of

spoiled vials are multiplied with the cost of the vaccine dose and the number of doses in each vial (δ_{sl}).

- Additional health workers costs are simply given as the multiplication of the summation of additional health workers employed ($AH_{vc,t}$) and their daily wage (σ).
- The rental cost of the fleet is given by the multiplication of the number of trucks required NT and the cost of each truck v.

$$
\begin{aligned}
min \quad & \sum_{h}\sum_{v}\sum_{c\in csv_{c,v}}\sum_{t} S_{h,v,t}\cdot\kappa_{c} + \sum_{vc}\sum_{v}\sum_{t} S_{vc,v,t}\cdot\kappa_{refrigerator} \\
& + \sum_{h}\sum_{vc\in HVC}\sum_{t} 2\cdot\mu_{h,vc}\cdot\left(\frac{\kappa\cdot\varphi}{100}\right)\cdot Y_{h,vc,t} + \sum_{h}\sum_{vc\in HVC}\sum_{t} 2\cdot\frac{\mu_{h,vc}}{\tau}\cdot o\cdot Y_{h,vc,t} \\
& + \sum_{vc}\sum_{v}\sum_{t} WD_{vc,v,t}\cdot\xi_{v} + \sum_{vc} WE^{I}_{sl}\cdot\delta_{sl}\cdot\xi_{sl} + \sum_{vc}\sum_{t} WE_{sl,t}\cdot\delta_{sl}\cdot\xi_{sl} \\
& + \sigma\cdot\sum_{vc}\sum_{t} AH_{vc,t} + \nu\cdot NT
\end{aligned}
\tag{5.29}
$$

In total, the developed MILP model for the cost minimization of COVID-19 VSCs comprises of constraints (5.1) to (5.28) and the objective function (5.29).

5.3.2 MILP-based solution strategy

For the solution of large, nation-wide problems, an MILP-based solution strategy, that utilizes a decomposition algorithm is employed. Let us assume a relatively small problem with one manufacturing plant, two hubs and 20 vaccination centres. The problem is decomposed employing the following rationale. First, the problem is divided into two subproblems, one for each hub, where the vaccination centres are pre-allocated to the closest hub. This assumption is motivated by the observation that in large problems, the vaccination centres will never be supplied by the hubs that are far away from them. So, this approach does not strongly affect the quality of the solution, however, it reduces immensely the combinatorial complexity of the problem, since many binary variables (connections of hubs to vaccination centres) are predefined. Next, the

vaccination centres are grouped into clusters based on existing political boundaries. As shown in Figure 5.4**,** four clusters are generated, two for each subproblem. The number of vaccination centres in a cluster may vary and it solely depends on the size of the political boundaries used. Then, the two subproblems are solved using the cluster entities, instead of the vaccination centres. To generate the models, all related parameters of the vaccination centres, e.g., vaccination targets, storage capacities etc. are aggregated to extract the parameters for each cluster. Through this aggregated approach, small problems are generated, that can be quickly solved. The solution of these models proposes optimal decisions considering the clusters as the last echelon of the vaccine supply chain. To disaggregate these decisions an additional step is introduced. Here, all binary variables are fixed, and the previous solution is used as a start point for the solver. This means that if in a time period t, the hub h is supplying vaccines to cluster cl ($Y_{h,cl,t} = 1$), then at this time period the hub will supply all vaccination centres of this cluster. Since, no binary variables are optimized, the model is reduced to an LP model, so it can be solved very fast.

Conclusively, the proposed solution strategy consists of two steps. In the first step, small subproblems are generated, first through a divide-and-conquer approach that creates MILP-subproblems for each hub, and then by an aggregation technique that reduces the number of involved entities, by grouping the vaccination centres into clusters. At this point the reduced MILP-subproblems are solved to provide optimal solutions for the clusters. In the second step of the algorithm, the binary decisions are fixed, and an LP-model is now solved for all vaccination centres. Sequentially, the MILP-subproblems for each hub are solved and finally the optimal plan for the entirety of the supply chain is created.

5.3.3 MILP-based replanning algorithm

Often citizens do not come to the planned appointment or reschedule their appointment at the last minute. This is a known issue in COVID-19 VSCs that must be considered, otherwise these variations between the planned and the actual vaccinations, may result to suboptimal or even infeasible solutions. Possible consequences could be the spoilage of numerous doses, the failure of achieving the vaccination targets, the violation of inventory limitations or the miscalculation of the needs in healthcare personnel. For

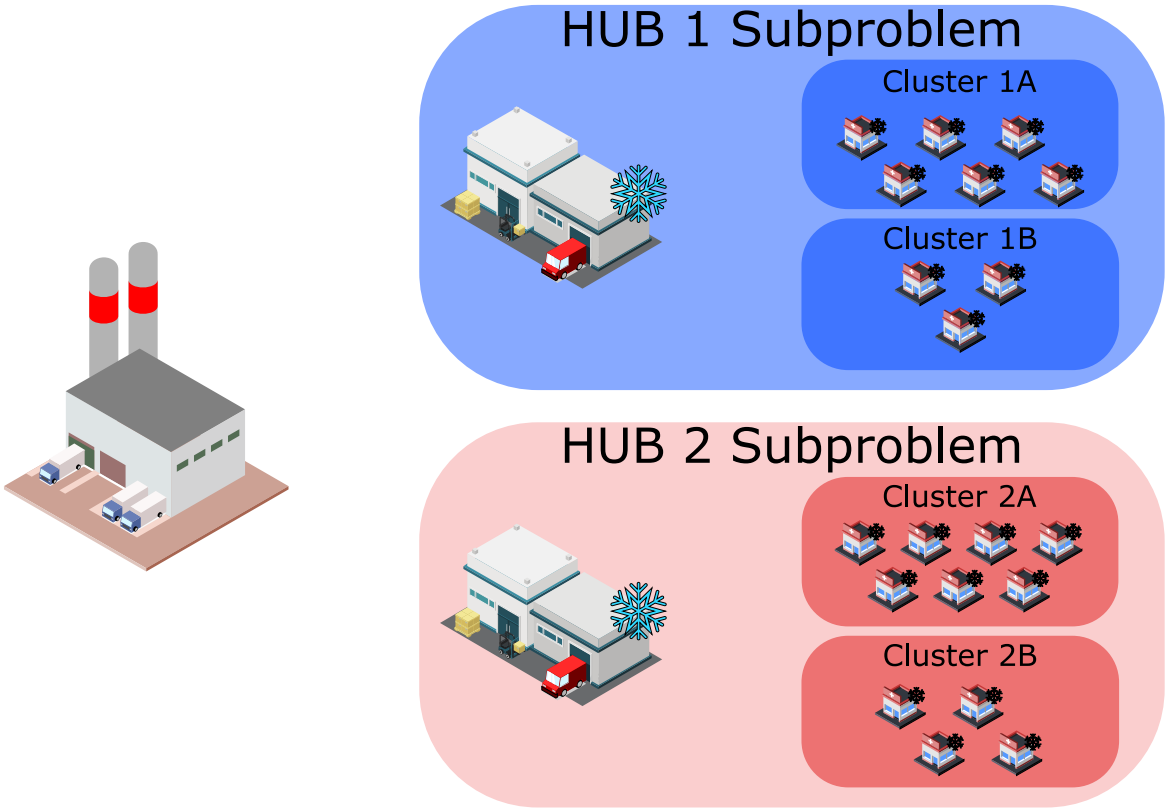

Figure 5.4: Decomposition approach

that purpose, a reactive approach can be employed, utilizing the aforementioned MILP-based solution strategy in the context of a rolling horizon algorithm, in order to ensure that the supply chain is properly replanned.

The introduction of four new subsets T_p, T_r, T_f and T_c is required for the implementation of the algorithm. T_p defines the prediction horizon, which includes all time periods considered by the optimization model at each iteration. In this study a bi-weekly prediction horizon is considered ($|T_p| = 14$). Fully reoptimizing the plan will provide the best possible solutions in terms of the underlying economic objective; however, it may require a significant number of changes, leading to nervousness, that could not be implemented in practice. Therefore, the prediction horizon subset is further divided into two subsets T_r and T_f. The first corresponds to the initial part of the prediction horizon, in which the decisions related to the binary variables ($Y_{i,j,t}$) and the daily number of vaccines used ($VU_{vc,v,t}$) remain fixed and equal to the previous solution. The second horizon is more flexible since the previous solution for the variables related

to the connections between locations of the supply chain and the vaccines used is applied as a lower bound. This ensures that the scheduled appointments will not be rescheduled, however more appointments or additional connections are possible to improve the quality of the plan. The length of these horizons can be freely chosen by the decision-makers based on their specific goals. In this study, equally length horizons are used ($|T_r| = |T_r| = 7$), which achieves a good trade-off between nervousness and solution quality. The rest of the variables, e.g., inventory profiles, transferred quantities etc., are fully relaxed throughout the prediction horizon. Finally, T_c corresponds to the control horizon, that includes all time periods, for which the optimized decisions are applied. Usually, the control horizon is set to a minimal of one time period, which allows the re-optimization of the plan after every time period ($|T_c| = 1$). The initial state of the supply chain in a given prediction horizon $T_{p,h}$ equals to the final state of the previous control horizon$T_{c,h-1}$. At the end of each time period the model receives the new information regarding the actual vaccination appointments and the new inventory levels at the vaccination centres.

Let us assume an illustrative example with the following horizon lengths, $|T_p| = 14$, $|T_r| = |T_r| = 7$, and $|T_c| = 1$ with initial time periods $\{t_1, \dots, t_{14}\}$, $\{t_1, \dots, t_7\}$, $\{t_8, \dots, t_{14}\}$ and $\{t_1\}$ accordingly. Initially the solution strategy computes the optimal plan for $T_p = \{t_1, \dots, t_{14}\}$. At this point the size of fleet is decided, which is the only decision variable that remains fixed. This decision remains fixed, since rental contracts are at least monthly, thus it would not be possible to change the fleet size intraweek. The plan will be implemented only for time period t_1. The information for the actual vaccinations done and the true levels of inventory in the vaccination centres becomes available at the end of the time period. The subsets are updated so that, $T_p = \{t_2, \dots, t_{15}\}$, $T_r = \{t_2, \dots, t_8\}$, $T_f = \{t_9, \dots, t_{15}\}$ and $T_c = \{t_2\}$. Using the new information and the previous solution, the proposed optimization-based solution strategy is employed. In particular, for time periods $\{t_2, \dots, t_8\}$ all binaries and the decisions related to the scheduled appointments remain fixed, while for rest of the time periods $\{t_9, \dots, t_{15}\}$ the previous solution is used as a lower bound. This procedure continues iteratively until the finalization of the vaccination program. So, in the employed rolling horizon algorithm the prediction horizon is moving forward in steps of $|T_c|$ time periods. Figure 5.5 illustrates the defined horizons for four consecutive iterations of the rolling horizon algorithm.

The implementation of this algorithm incorporates uncertainties of the COVID-19 supply chain related to the differences between the planned and the actual appointments in the modelling approach. Thus, the decision-makers can deal with such uncertainties and constantly improve the extracted plans using the current state of the supply chain. Decisions related to transferred quantities, employed healthcare personnel and inventories can be promptly adjusted to include any new information, ensuring the success of the vaccination program, while minimizing the total operational costs.

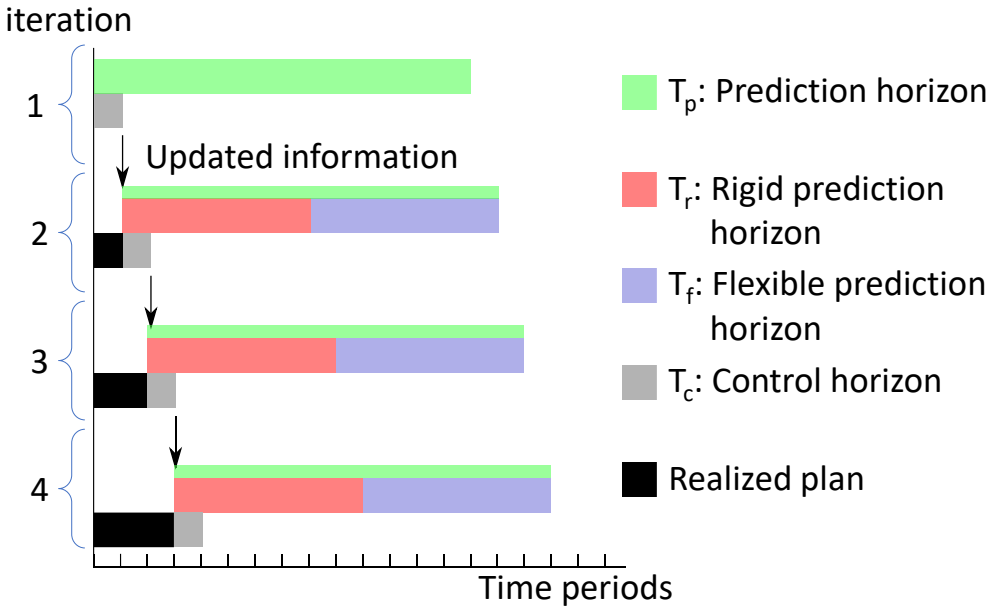

Figure 5.5: Replanning via a rolling horizon approach

5.4 Results

In this section the developed optimization-based framework is tested. First, an illustrative example is used to test in detail the efficiency of the proposed MILP-model. Then, a large-scale problem that simulates the Greek COVID-19 VSC is studied, and near-optimal planning decisions are generated by employing the proposed MILP-based solution strategy. Finally, the applicability of the replanning algorithm is illustrated even for extreme disturbances in the vaccination plan. All models and solution algorithms were developed using the GAMS 30.1 interface and all instances were solved in an Intel Core i7 @3.4Gz with 16GB RAM using the commercial solver CPLEX (Brooke et al. 1998).

5.4.1 Illustrative example

Let us assume a COVID-19 supply chain consisting of one hub and five vaccination centres. Two vaccines (P and M) are available, supplied by two manufacturing plants. Each plant is exclusively producing and supplying to the hubs only one vaccine type. A 14-days horizon is considered, and all related data e.g. storage capacities, vaccination goals, distances etc. are provided in Appendix C (Table C.1 – Table C.6). The Pfizer-type vaccine can be stored for up to 5 days in the vaccination centres, while perishability constraints are not enforced on the Moderna-type vaccine, whose shelf-life in refrigerated conditions (30 days) greatly exceeds the planning horizon. The daily ratio of stored vaccines is set to 0.25% for the hubs and 1% for the vaccination centres. It is assumed that the Pfizer-type vaccines included in the initial inventory ($\alpha_{vc,v}$) of the vaccination centres have just been transferred.

The developed MILP model is employed to minimize the total cost for the distribution of the vaccines and the scheduling of the vaccination program in the vaccination centres. For the examined problem instance, the model consists of 1623 variables, 363 of them binary, and 1595 equations. Within 30 CPU seconds, an optimal solution with a minimum cost of 22059 RMUs[1] is generated. The most significant costs are associated with the operation of the storage technologies, especially the freezers and deep freezers in the hubs. In particular, 59.8% of the total costs originate from storing the vaccines in the hubs and 19.1% are due to storage costs in the refrigerators of the vaccination centres. Thus, inventory costs comprise the 78.9% of the total cost, emphasizing the importance of generating decisions that optimize the inventory profiles of the supply chain. Regarding the rest of the cost terms, the ones related to the transportation of the vaccines, specifically the fuel costs, the drivers' wages, and the rental cost for the trucks, cover 3.8%, 9.3% and 6.1% of the total cost accordingly. Only 26 doses are lost translating to 1.8% of the total costs. Notice that no additional healthcare personnel are used, therefore the associated cost term is zero. Table *5.1* reports the number of vaccine vials stored in the hub and the vaccination centres throughout the considered horizon ($S_{i,v,t}$). Further detailed results on the vials transferred ($X_{i,j,v,t}$), the vials opened ($VU^{I}_{i,v,t}$), the doses used ($DU_{i,v,t}$), the daily

[1] Relative Monetary Units

appointments ($DA_{i,t}$), the solution statistics and the cost distribution are found in Tables 5.2 – 5.6.

Table 5.1: Stored vials in the hub and in the vaccination centres ($S_{i,j,t}$)

		t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14
H	**P**	3	3				975	21	21	3	2	977	240	240	240
H	**M**		735						1234	269	242	242	242	242	242
C1	**P**	5	2	1				332	184	42	7	4	289	289	289
C1	**M**	177	89	254	166	77	6	6	3	333	264	175	87	87	87
C2	**P**	98	2	2	1	1	1	276	138	7	2	1	213	213	213
C2	**M**	105	80	244	161	79				320	238	155	74	74	74
C3	**P**	88		1				176	87	3			138	138	138
C3	**M**	51	50	157	103	50				207	154	100	47	47	47
C4	**P**	56	12	9	5	4		95	50	9	5	1	68	68	68
C4	**M**	23	22	72	47	20				99	73	48	23	23	23
C5	**P**	15						67	46	26	12		31	31	31
C5	**M**	56	53	40	27	15	3	3	3	2	25	20	8	8	8

Table 5.2: Vials opened ($VU^{l}_{i,v,t}$)

		t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14
C1	**P**	88	3	1	1				148	148	35	1		148	
C1	**M**	36	86	88	88	89	71				68	88	88		
C2	**P**	81	96	1	1				136	136	5	1	1	136	
C2	**M**	33	24	81	81	81	79				79	81	81		
C3	**P**	53	88		1				88	88	3	0		88	
C3	**M**	21		51	52	52	50				51	52	53		
C4	**P**	24	44	4	4	1	4		44	44	4	4	3	44	
C4	**M**	12		24	24	26	20				24	24	25		
C5	**P**	10	15						20	20	15	12		20	
C5	**M**	6	3	12	12	12	12				3	4	12		

Table 5.3: Doses used ($DU_{i,v,t}$)

		t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14
C1	**P**	528	18	6	6				888	888	208	6		886	
C1	**M**	360	860	880	880	888	710				680	880	880		
C2	**P**	486	576	6	6				816	816	26	6	6	816	
C2	**M**	330	240	810	810	810	790				790	810	810		
C3	**P**	318	528		6				528	528	18	0		528	
C3	**M**	210		510	520	520	500				510	520	528		
C4	**P**	144	264	24	24	4	24		264	264	24	24	14	264	
C4	**M**	120		240	240	260	200				240	240	250		
C5	**P**	60	90						120	120	90	72		120	
C5	**M**	60	30	120	120	120	120				30	40	120		

Table 5.4: Daily appointments ($DA_{i,t}$)

	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14
C1	888	878	886	886	888	710		888	888	888	886	880	886	
C2	816	816	816	816	810	810		816	816	816	816	816	816	
C3	528	528	510	526	520	520		528	528	528	528	528	528	
C4	264	264	264	264	264	264		264	264	264	264	264	264	
C5	120	120	120	120	120	120		120	120	120	120	120	120	

Table 5.5: Solution statistics

CPU (s)	Variables	Binary Variables	Equations	Solution (RMU)	Gap
30	1623	363	1505	220059	<5%

Table 5.6: Cost distribution

Storage cost in hubs	Storage cost in clinics	Fuel cost	Drivers cost	Cost of wasted doses	Cost of trucks
13194	4213	836	2058	408	1350

5.4.2 Large-scale case study: The Greek COVID-19 VSC

In order to evaluate the developed MILP-based framework for realistically-sized COVID-19 supply chains, the problem of the panhellenic vaccination program is simulated. At the time of writing this paper, the Greek state is using five hubs in total. Due to security reasons the exact locations of these hubs are unknown. However, it is known that two are in the region of Attica, near Athens, one is in the region of Thessaloniki, one in the region of Karditsa and one in Crete. Based on this knowledge the locations of the hubs are approximately chosen. The hospitals and health centres of Greece as provided by the Hellenic Ministry of Health are used as vaccination centres. Except for Crete, which has its own hub, Greek islands are not taken into account in the study. As a result, a total of 351 vaccination centres, each consisting of multiple vaccination lines, are considered. Four vaccine types are available (P, M, A, J) each one produced and supplied exclusively by a single manufacturing plant. Conclusively, the supply chain consists of four manufacturing plants, five hubs and 351 vaccination centres. To create the required data, the population data of Greece from the Population and Housing Census conducted by the Hellenic Statistical Authority are used (Hellenic Statistical Authority 2011). The population is divided based on the regional unity and the vaccination centres are allocated to their respective regional unit. Four types of vaccination centres, more specifically hospitals, large, medium, and small health centres, that differentiate on the daily vaccination capacity, are considered. A relevant vaccination capacity between them is assumed. Each hospital, large and medium health centre has the capacity of 8, 4 and 2 small health centres accordingly. Based on this information, the total vaccination demand for each centre has been calculated. To generate the vaccination targets for the considered horizon of 14 days, it is assumed that the vaccination program for the entirety of the population must be realized within 6 months. So, the total demand for each vaccination centre is divided by 12 to get the bi-weekly vaccination targets. The straight-line distances between the hubs and the vaccination centres are calculated from google

maps. They are then approximately converted to real distances (using roads) by multiplying them with 1.417, as proposed in Boscoe et al. (2012). According to this contribution, if errors up to 10 percent or 10 kilometres are accepted, then the approximation above is accurate for 96% of the cases. To ensure the feasibility of the problem, the initial inventory in the hubs and the vaccination centres is enough to satisfy at least the vaccination demand of the first two time periods. Otherwise, the required lead time would make it impossible to supply the necessary vaccines to the centres on time. It is assumed that Pfizer vaccines in the initial inventory arrived the day prior to the start of the considered horizon. Vaccine inventories in the manufacturing plants are not considered as they are irrelevant for the problem under consideration.

The above problem is solved by employing the proposed MILP-based solution strategy. Each vaccination centre is allocated to a single hub based on the geographical criteria. For the first aggregation step of the solution algorithm, the 351 vaccination centres are grouped into 54 clusters based on their regional unit. Detailed data of the considered problem instance e.g., maximum vaccine supply, distance matrix, hub to vaccination centres connectivity and vaccination centres to clusters allocation, are provided in Tables C7 - C12 of Appendix C. To generate near-optimal solutions for the entirety of the supply chain, five individual subproblems, one for each hub are solved. First the clusters are considered, and aggregate solutions are proposed and then the detailed solutions for all vaccination centres of the subproblems are created. The solver terminates either when the computational time limit of one hour (3600 seconds) is exceeded, or when an optimality gap of 5% is achieved. Table *5.7* portrays the solution statistics for all iterations of the individual subproblems. It is shown that the computational time limit is reached for the more complicated cases (H1, H2 and H3) in the first step of the solution strategy. However, the optimality gaps achieved are very close to the desired target. It must be noticed that for these cases relatively good optimality gaps (15%-20%) were achieved in very low CPU times, of around 15 minutes, displaying the model's capability of quickly proposing good solutions for complex problems. On the contrary, subproblems H4 and H5 are promptly solved to optimality. The time required for the second step is very low in comparison. Even the most difficult subproblem (H1) is resolved within three minutes. This is expected, since all binary variables are fixed, reducing the problem into a simple LP. Comparing the problem sizes of the first and second step it is observed that the aggregated approach significantly

reduces the number of variables and equations, making the consideration of large and complex problem instances feasible. The computational time required in total is close to 3.5 hours, however the utilization of parallel computing techniques reduces it to around 1 hour.

Table 5.7: Solution statistics for the Greek case study

First step (Aggregate solution)						
	CPU	Variables	Binary Variables	Equations	Solution	Gap
H1	3600	18993	986	12269	283808	7%
H2	3600	15073	986	10309	189815	8%
H3	3600	13421	738	8845	171274	8%
H4	25	13323	614	8477	384564	<5%
H5	1365	4846	304	3441	65194	<5%
Second step (Detailed solution)						
	CPU	Variables	Binary Variables	Equations	Solution	Gap
H1	158	47391	5088	41731	291435	<1%
H2	71	32446	3408	28431	192462	<1%
H3	25	32425	3456	28587	176151	<1%
H4	13	35190	3792	31135	387297	<1%
H5	1.6	10718	1104	9575	66164	<1%

Figure 5.6 displays the distribution of the various cost terms for the case study of Greece. Similar conclusions to the ones for the illustrative example can be drown. Storage costs in the hubs and the vaccination centres are the most significant terms, comprising together the 78% of the total costs. Next come the transportation costs, more specifically the wage of the drivers (9%), the cost of renting the trucks (8.4%) and the cost of fuel (3.8%). Finally, very few doses are lost (0.7%), while extra healthcare workers are rarely required (0.3%). The precise cost distribution for each of the five subproblems solved are provided in Table 5.8.

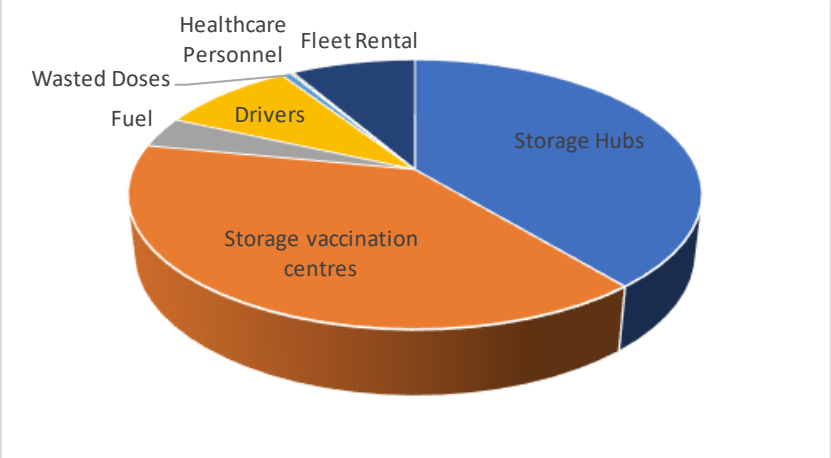

Figure 5.6: Cost distribution for the Greek COVID-19 VSC

Table 5.8: Detailed cost distribution for each hub of the Greek COVID-19 VSC

	Storage Hubs	Storage Centres	Fuel	Drivers	Wasted Doses	Healthcare Personnel	Fleet Rental	Total
H1	109571	110123	11722	28855	1791	753	28620	291435
H2	59040	77979	10461	25751	1321	359	17550	192461
H3	40694	75248	11041	27179	2169	381	19440	176152
H4	199633	144638	5781	14231	1272	412	21330	387297
H5	25382	26486	2144	5278	379	285	6210	66164
Total	434320	434474	41149	101294	6932	2190	93150	1113509

Figure 5.7 illustrates the inventory profiles in each of the hubs and aggregated for all vaccination centres. It is noticed that the stored amounts are sustained relatively low to reduce as much as possible the storage costs. This is especially evident for the Pfizer and Moderna-type vaccines, which consistently do not remain in storage, rather they are used as fast as possible. This is expected since the mRNA vaccines are stored using special technologies that impose high operational costs. The stored amounts are increased in the end of the horizon to satisfy safety stock requirements. Low quantities of Pfizer-type vaccine are observed in the inventory profiles of the vaccination centres which ensure that the vaccines are not spoiled due to perishability issues. Moreover, the inventories of the vaccination centres at the end of Saturdays (time periods 6 and 13) are practically zero since it is assumed that no vaccinations are done on Sundays.

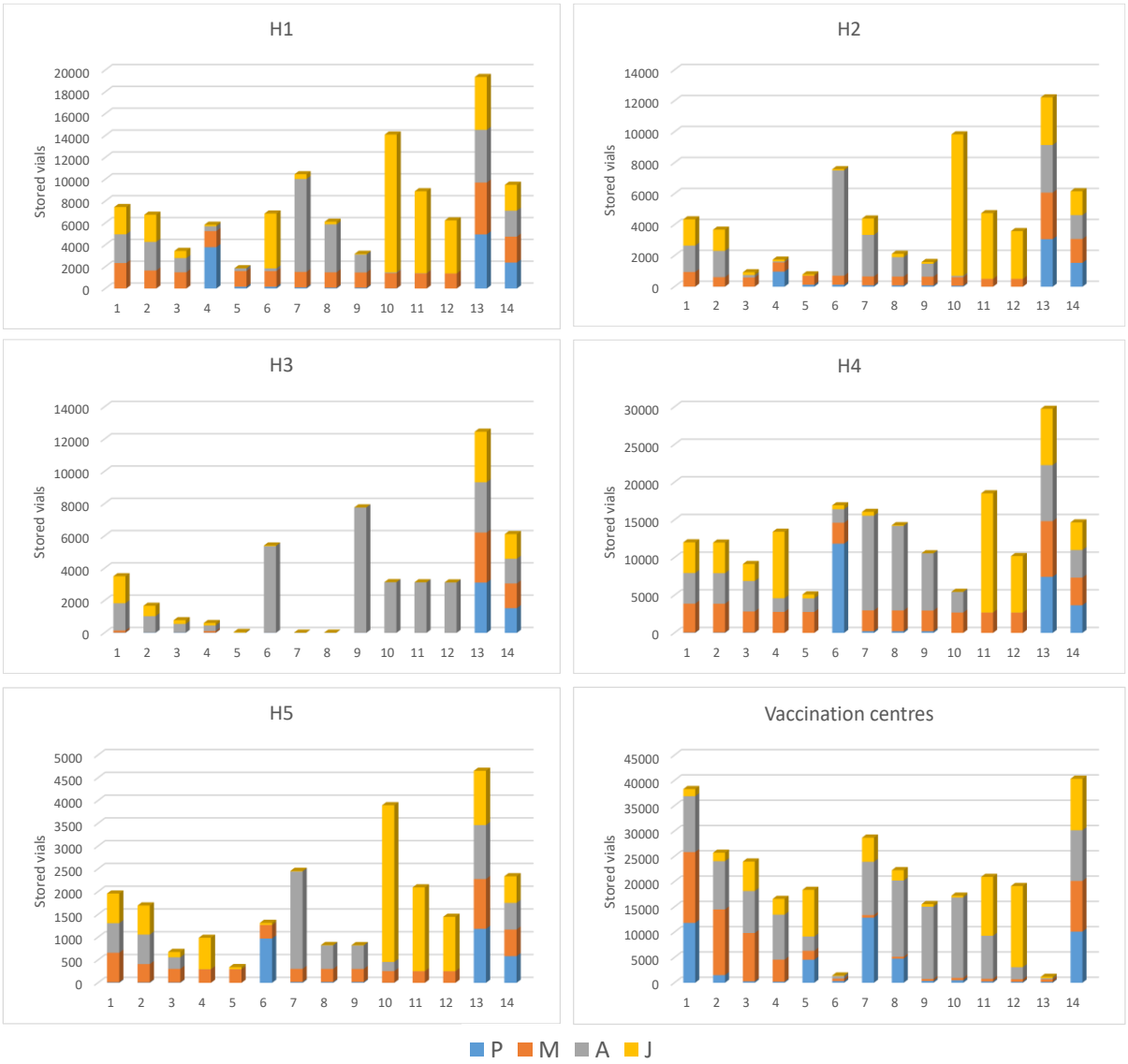

Figure 5.7: Inventory profiles in hubs and vaccination centres

In the study so far, it was assumed that the fleet size is unbounded. Therefore, a sensitivity analysis is done to show the effects that the size of the homogeneous fleet size has on the solution quality. Five scenarios with varying upper bound of fleet size are solved for all subproblems. The maximum number of rented trucks is defined as a percentage of the total connections between each hub and the vaccination centres. For the five scenarios studied, this percentage is set to 100%, 90%, 80%, 70% and 60%. For example, if a problem consists of 100 vaccination centres, then the maximum number of rented trucks will be 100, 90, 80, 70 and 60 in the different scenarios. Figure 5.8 displays the results of this analysis. The y-axis portrays the relevant difference a solution has to

the optimal one. For example, if a hub with a specific fleet availability has a y-value of 1.1, then the total cost is 10% higher than the lowest found. As expected, the best solution is always provided, when the fleet size is unbounded. A clear correlation is observed in all subproblems. Lowering the maximum allowed fleet size has a negative effect on the solution, meaning that the cost of the supply chain increases. However, the effect is significant (>5%) only for extreme cases, where the fleet size is strongly bounded (60% of possible connections).

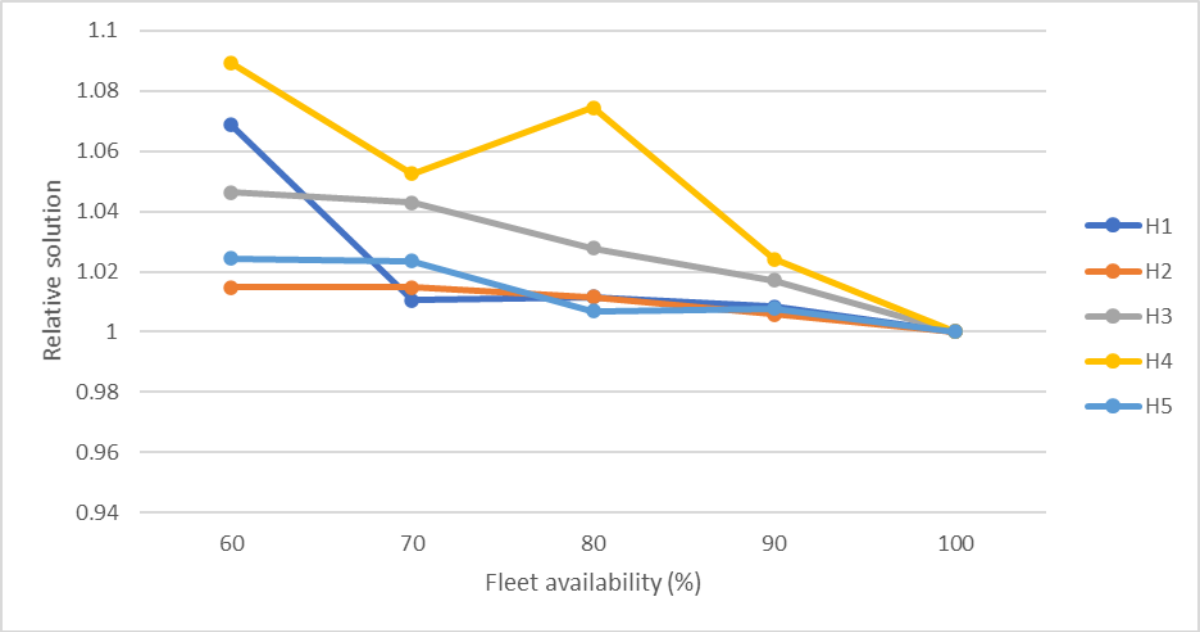

Figure 5.8: Sensitivity analysis on fleet size

5.4.3 Replanning the COVID-19 VSC

In this subsection the problem of replanning the COVID-19 supply chain in cases of disturbances due to citizens not arriving to scheduled appointments is studied. The MILP-based replanning technique is implemented to deal with such unexpected alteration in a reactive manner.

The case study used replicates the subproblem of hub H1 from the Greek nationwide problem presented in the previous section. First, the model is solved for the initial 14-day horizon. At the end of the first period, the decision makers gather the following information. All scheduled appointments were completed in only 26

vaccination centres. In 15 of them 5% of the appointments were not realized, while 10% and 15% of the citizens did not arrive in the appointments in 44 and 21 vaccination centres accordingly. Similar alterations between planned and actual appointments occurred in the next two periods. In the second period, the percentage of unrealized appointments was 2% in 45, 8% in 11 and 12% in 30 centres, while on the third period these were 4% in 30, 10% in 40 and 25% in 6 vaccination centres. Those disturbances call for the immediate replanning of the supply chain since the actual inventory profiles are significantly different to the planned ones. Therefore, when the new information becomes available, the proposed solution strategy is employed to reactively replan the supply chain. The cost distribution after every iteration of the solution algorithm is shown in Table 5.8. It is shown that the costs remain low, despite the significant disturbances. Interestingly, very few doses are wasted, while storage costs are not increased, showing the flexibility of the proposed solutions in case of unexpected disturbances, as well as the efficiency of the reactive strategy.

Table 5.9: Cost distribution for every iteration of the rolling horizon algorithm

Iter	Storage Hubs	Storage Centres	Fuel	Drivers	Wasted Doses	Healthcare Personnel	Fleet Rental	Total
1	27202	47520	7548	18580	846	954	21330	123981
2	22703	44329	6280	15457	1337	1080	21330	112517
3	24401	37839	5442	13395	803	1018	21330	104228
4	24202	37367	5676	13971	791	1022	21330	104359

An interesting observation can be made regarding the wasted doses, the large majority of which are Astrazeneca-type vaccines. Very few Pfizer-type and Johnson & Johnson-type vaccines are spoiled, while nearly no Moderna-type vaccines are wasted. The model correctly prioritizes the use of the costly mRNA vaccines, although very few Pfizer-type vaccines are lost due to their limited shelf-life and the least expensive alternative (Astrazeneca-type vaccines) is chosen to be wasted. Detailed information on the wasted doses per iteration are given in Table 5.10.

Table 5.10: Number of wasted doses with disturbances in the vaccination plan

Iter	Wasted doses			
	P	M	A	J
1	2	0	228	49
2	39	1	454	5
3	3	0	431	0
4	7	0	378	4

5.5 Conclusions

In this chapter, the optimal planning of the COVID-19 VSC is considered. Specific problem characteristics, such as special cold storage requirements, extremely limited shelf-life of some vaccine types in refrigerated conditions and the unprecedented time pressure for the realization of the vaccination program, differentiates it from other supply chain problems. To the best of our knowledge, this is the first work to address the planning problem of the COVID-19 vaccine distribution chain in an integrated manner. Furthermore several extensions have been made by integrating various decisions related to optimally planning the daily vaccination program in every vaccination centre. A novel MILP model is developed to tackle this integrated problem. The efficiency of the proposed model is first illustrated in a small example. Optimal decisions leading to the minimization of total cost are generated in very low CPU times. Furthermore, a decomposition strategy is developed to extend the applicability of the model on realistically sized problems. A simulated instance of the Greek COVID-19 VSC is used to illustrate the capabilities of the proposed framework. Decisions on the transferred vaccine quantities, inventory profiles, transportation, and staff requirements, as well as, daily vaccination plans, for a nationwide problem, are optimally taken in low CPU times. Finally, a reactive approach that utilizes a rolling horizon algorithm is proposed to handle uncertainties related to unexpected disturbances in the daily vaccination plan of the vaccination centres.

Nomenclature

Indices

i, j	Locations (manufacturing plants-hubs-vaccination centres)
v	Vaccine
c	Cold storage technology
t	Time periods
w	weeks

Sets

f_i	Manufacturing plants
h_i	Hubs
vc_i	Vaccination centres
cl_i	Clusters
FV	Vaccine *v* produced in manufacturing plant *f*
IJ	Connectivity between the locations of the supply chain
HVC	Connectivity between hubs *h* and vaccination centres *vc*
CV	Cold storage technology *c* necessary for long term storage of vaccine *v*
SL_v	Subset of vaccines that have a shelf-life smaller than the considered horizon

Parameters

$\pi_{h,v}^{max}$	Maximum supply of vaccine *v* to hub *h (vials)*
$\alpha_{i,v}$	Initial stored amount of vaccine *v* in location *i (vials)*
β_i	Ratio of vaccine *v* wasted in location *i*
$\gamma_{h,c}$	Storage capacity of technology *c* in hub *h (vials)*

θ_{vc}	Storage capacity in vaccination centre *vc (vials)*
$\varepsilon_{i,v}$	Safety stock of vials *v* in location *i*
$\rho_{i,j}^{min}$	Minimum flow allowed between a locations *i* and *j*
$\rho_{i,j}^{max}$	Maximum flow allowed between a locations *i* and *j*
δ_{v}	Doses per vial of *v*
λ_{v}	Shelf-life of *v* in refrigeration *(days).* Only relevant for vaccines with a shelf-life smaller than the considered horizon.
ζ_{vc}	Vaccination goal for each vc
η	Number of vaccinations done daily by a vaccination line (Two health workers)
ι_{vc}^{max}	Maximum number of healthcare workers in vaccination centre
ι_{vc}^{b}	Base number of healthcare workers in vaccination centre
ψ_{c}	Operating cost of cold storage technology *c (€ per daily storage of a single vial)*
κ	Average fuel consumption of truck transporting vaccines *(litres per 100 km)*
φ	Fuel price *(€ per litre)*
$\mu_{i,j}$	Distance between location *i* and *j (km)*
τ	Average speed of vehicles transferring the vaccines
o	Cost of employing a driver *(€/hour)*
ξ_{v}	Cost of vaccine *v (€/dose)*
σ	Cost for utilizing extra healthcare workers (daily)
ν	Cost of renting a truck (Two weeks)

Variables

$X_{i,j,v,t}$	Amount of vaccine *v* transferred from location *i* to *j* in period *t (vials)*

$S_{i,v,t}$	Amount of vaccine *v* stored in location *i* in period *t (vials)*
$P_{f,v,t}$	Amount of vaccine *v* supplied by manufacturing plant *f* in *t (vials)*
$LS_{i,v,t}$	Wasted vials of vaccine *v* in location *i* in time period *t*
$VU_{vc,v,t}$	Vials of vaccine *v* used in *vc* in period *t*
$L_{vc,v,t,t'}$	Amount of vaccine v *(vials)* transferred in *vc* in *t* and used in *t'*
$WD_{vc,v,t}$	Wasted doses of vaccine *v* in vaccination centre *vc* in period *t*
$DU_{vc,v,t}$	Doses of vaccine *v* used in *vc* in period *t*
$DA_{vc,t}$	Vaccination appointments in location *i* in time period *t*
$VA_{i,v,t}$	Appointments using vaccine *v* in location *i* in time period t
$WE_{i,t}$	Vials of vaccine v wasted due to expiration in location *i* in time period *t*
WE_{i}^{I}	Vials of initially stored vaccine wasted due to expiration in location *i* in time period *t*
$HW_{i,t}$	Number of health care workers required in location in location *i* in time period *t*
$AH_{i,t}$	Additional health workers (more than base) required in location *i* in time period t
NT	Number of trucks required for transportation
$SU_{vc,slv,t}$	Vials of initially stored vaccine *slv* used in *vc* in period *t*
$VU_{vc,v,t}^{I}$	Integer number of vials of vaccine *v* used in period *t*
$Y_{i,j,t}$	Equals 1 if vaccines are transferred between locations *i* and *j* in period *t*

Chapter 6

Conclusions and Future Research

6.1 Conclusions

The objective of this thesis has been to develop optimization-based techniques to address the production planning and scheduling problem of complex industrial processes and the short-term planning of the COVID-19 VSC. Various instances of a mixed-integer linear programming (MILP) modelling framework have been developed in combination with novel heuristic methods and solution strategies for large-scale industrial problems. Applying the research output of this thesis in real-life problems is expected to have a significant economic and environmental impact.

Chapter 2 studied the optimal production scheduling problem of industrial facilities comprising of both batch and continuous processes. Several literature contributions have already proposed solution methods to address this known problem, since this is a common plant layout in many industrial sectors. However, their focus was on the solution of small to medium problems of specific complexity. The combinatorial complexity of this problem is such that the generation of optimized schedules for large-scale problems is extremely difficult. Therefore, two alternative methods have been proposed, which can effectively address even the most challenging problems often met in industrial applications. The specific industrial case includes two continuous processes with a sterilization process in between. Both approaches consist of two subsequent steps. First a batching algorithm translates the incoming orders into production batches that need to be scheduled and then a novel MILP-based decomposition method is used to solve the optimal production scheduling problem. In the first approach, an MILP model based on the general precedence framework is developed to minimize the production makespan. A cyclic allocation heuristic has been introduced to decrease the problem's combinatorial complexity. To further accelerate the solution method, we incorporated the model within a bi-level decomposition algorithm that optimizes the schedules for one time period and a subset of orders in each iteration. In the second approach a novel

aggregation method is introduced that incorporates a set of feasibility constraints for the sterilization stage. This reduces the production into a two-stage continuous process thus enhancing its efficiency. Based on this rationale two MILP modes, one for makespan minimization and one for changeover minimization were developed. A new order-based decomposition algorithm is proposed that is characterized by increased flexibility, thus providing near-optimal solutions. We have shown that both solution strategies can successfully address the problem at hand.

Chapter 3 is a direct continuation of the previous chapter and places particular emphasis on the successful implementation of the developed mathematical frameworks in a production scheduling problem of a real-life food industry. The overall scheduling problem is characterized by a significant combinatorial complexity, since more than 100 products must be processed within the scheduling horizon. Real operational and demand data have been used as extracted by the MES and the ERP system for several historical production weeks. Both approaches were able of providing near-optimal solutions in relatively low computational times. It was shown that the developed solution methods have distinct strengths. Approach A addresses problem instances where the facility needs to shut down at the end of each day, while it generates detailed schedules for all processing stages. In contrast, approach B which can also address the changeover minimization objective, is computationally superior to approach A, however, it does not provide detailed scheduling decisions for every processing stage. A comparative study between the proposed optimized schedules and the ones generated manually by the production engineers, illustrates the superiority of the developed mathematical frameworks. Improvements of approximately 10% to 15% are reported in the production makespan and the total changeover time, depending on the overarching goal of the model used. The proposed optimization framework can be easily extended to address similar large-scale scheduling problems. Moreover, the extraction of validated results for industrial cases that directly use real-life data, make the proposed strategies suitable for the development of computer-aided scheduling tool, that will facilitate the production engineers into taking better and fast decisions.

Chapter 4 is considered with the integrated production planning and scheduling problem of breweries. The special characteristics of the beer production process, mainly the long lead times due to the required fermentation process, does not allow for the direct

application of the methods presented in Chapter 2. To efficiently address the underlying problem, the main production bottlenecks, were solely modelled, namely the fermentation process and the filling process, without loss of significant accuracy. Consequently, the production procedure is reduced into a two-stage production, consisting of a batch and a continuous process. A novel MILP model based on the immediate precedence framework was developed. A mixed discrete-continuous time representation is employed, in which the discrete time grid is used to monitor inventories and backlogs, while in the continuous time representation all necessary scheduling decisions, e.g. allocation, timing and sequencing, are considered. To allow the examination of longer time horizons, two subsets of time periods were considered. In the first, detailed scheduling and planning decisions are taken, while in the second only planning decisions are extracted. It was showed that the developed model provides superior schedules compared to the only other relevant optimization method found in the open literature. In order to extend the applicability of the method in large-scale problems, which better simulate the industrial reality, the proposed model was incorporated into a novel decomposition algorithm. This consists of a constructive and an improvement step. In the first step an initial good solution is promptly generated by spatially decomposing the studied problem, which is iteratively enhanced in the latter step. Improving the initial solution is done by a set of fix-and-optimize heuristics, which first relax a subset of the considered variables through spatial and/or temporal decomposition and then reoptimize it. Multiple case studies were used to illustrate the efficiency and applicability of the proposed methods towards high quality solutions in low CPU times. A real-life case study inspired by a Greek brewery was additional used for the application of the optimization frameworks.

Finally, in chapter 5 the scope of this thesis was extended by considering the emerging topic related to the planning of the COVID-19 VSC. This is one of the first contributions in the open literature to study the problem of simultaneously providing optimal short-term planning decisions for the VSC (e.g. inventory levels, vaccine flows etc.) and decisions related to the optimal vaccination plans of the citizens in the vaccination centres. An MILP model was developed to model this integrated problem. All special characteristics related to the COVID-19 VSC, such as the requirements of special cold storage technologies, the limited shelf-life of mRNA vaccines in refrigerated conditions and the extreme time pressure for the realization of mass vaccination

programs, are taken into account. The proposed model generates optimal decisions on the inventory levels, flows, vaccine orders, the required fleet size and the needs on healthcare personnel so that the total cost of the supply chain is minimized. The economic objective includes the storage costs, the cost of transportation (fuel and drivers' wages), the cost for additional healthcare workers and the cost of wasted doses. A small example problem first illustrates the efficiency of the model by generating fast optimal solutions and underlines its inability of handling complex, real-life nation-wide vaccination programs. Therefore, an efficient solution strategy was proposed. According to this, first a number of subproblems are systematically created according to a divide-and-conquer approach and then an aggregation technique clusters the vaccination centres, to reduce the associated binary decisions. Finally, a set of LP subproblems are solved to take detailed decisions for all supply chain nodes involved. The above strategy is successfully tested in a large case study that simulates the Greek COVID-19 VSC. In relatively short CPU solutions times near-optimal solutions are derived for the entire VSC. A comprehensive computational analysis illustrated that the dominant cost factor is related with the cost for vaccines' storage. Finally, a rolling-horizon algorithm was proposed to consider disturbances in the vaccination schedule originating mainly from citizens cancelling or not arriving on scheduled appointments. Several tests have shown that even in extreme situations, very few valuable doses are wasted by solving the integrated vaccine supply chain distribution planning problem.

6.2 Main contributions of this work

In summary, the main contributions of this thesis have been:

- Two novel mathematical programming frameworks have been developed for the optimal production scheduling of mixed batch and continuous processes. Approach A introduces a new set of allocation heuristic constraints, while approach B proposes an aggregation technique based on novel feasibility constraints for the batch stage. As a result, the developed models are characterized by increased efficiency. Both makespan and changeover minimization have been explored.

- Efficient solution strategies, which comprise of a pre-processing algorithm, the proposed MILP models for optimal production scheduling in mixed batch and continuous processes and a decomposition algorithm, have been developed, to address large-scale case studies. A bi-level temporal/order-based decomposition is applied in approach A, while a novel, flexible order-based decomposition technique is proposed in approach B. The computational analysis underlined the efficiency and applicability of the developed solution strategies.
- Application of the developed mathematical frameworks in a real-life industrial problem. Significant benefits due to the integrated optimization of several production stages have been revealed. Rather than undergoing the laborious task of manually generating sub-optimal schedules, the developed solution algorithms can assist production engineers and managers towards fast generation of improved schedules. Several instances of a real-life food industrial case study have been introduced in the open literature.
- A mixed-integer programming model for the integrated optimal production planning and scheduling of breweries have been developed. It has been shown that the proposed method is superior to the alternatives found in the open literature. Furthermore, a novel two-step decomposition algorithm have been developed to consider large-scale problems.
- The introduction of efficient solution methods for large-scale problems and their successful implementation in real-life problems are important steps into closing the existing gap between scientific knowledge and industrial reality.
- The optimal short-term planning problem of the COVID-19 VSC has been introduced in the open literature. The first mathematical model to address this problem have been developed, while a two-step solution strategy has been proposed for the consideration of nation-wide problems. Optimal operational decisions of the VSC that minimize an economic objective are generated in low CPU solutions times. The developed mathematical framework can facilitate nation-wide VSCs and ensure the success of large vaccination programs.

6.3 Recommendations for future directions

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

- The methods proposed in Chapter 2 are limited by the fact that the sterilization chambers must be identical. The consideration of a more general sterilization stage whose equipment have different characteristics will further extend the applicability of these mathematical frameworks.
- The main drawback of the aggregated approach presented in Chapter 2 is the generation of decisions solely for the continuous stages. Therefore, a step that creates feasible detailed decisions for the sterilization stage could be added.
- In many breweries buffers are used between the liquid preparation and the liquid bottling stages, as intermediate storage for the ready liquid. Extending the developed mathematical framework so that these buffers can be efficiently modelled is expected to further improve the plant's productivity.
- The main focus of this thesis have been the offline scheduling of complex optimization problems. Since production scheduling is highly dynamic, the incorporation of real-time uncertainties in the developed models is critical for their application in real-life situations. A computationally efficient method is the introduction of a reactive scheduling approach that employs a rolling-horizon algorithm.
- A computer-aided tool which uses as core the proposed mathematical frameworks can be developed to tackle industrial scheduling problems in real time. Possible issues are expected to be ensued and their resolution will rectify the benefits reaped from the developed optimization methods.
- Room for improvement exists regarding the solution strategy developed for the COVID-19 VSC. More sophisticated clustering techniques, e.g. k-means algorithm, will enhance the effectiveness of aggregating the vaccination centres into clusters. Furthermore, an additional step can be added to reoptimize the solution generated by the divide-and-conquer approach. After generating the initial solutions, critical binaries can be relaxed and reoptimized. These binaries represent connections between nodes for clusters that are between multiple hubs. This will add flexibility to the method allowing for higher quality solutions.

Further improvements are expected by integrating tactical and more detailed operational decisions, such as, vehicle routing decisions.

- Finally, the mathematical frameworks developed in chapters 4 and 5 can be applied to real-life problems of breweries and COVID-19 VSC accordingly.

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Research Outputs

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

Peer-reviewed journal publications

1. Georgios P. Georgiadis, Georgios M. Kopanos, Antonis Karkaris, Harris Ksafopoulos and Michael C. Georgiadis (2019). "Optimal Production Scheduling in the Dairy Industries." *Industrial and Engineering Chemistry Research*, 58, 6527-6550

2. Georgios P. Georgiadis, Apostolos P. Elekidis and Michael C. Georgiadis (2019). "Optimization-Based Scheduling for the Process Industries: From Theory to Real-Life Industrial Applications." *Processes*, 7(7), 438, https://doi.org/10.3390/pr7070438

3. Georgios P. Georgiadis, Borja Mariño Pampín, Daniel Adrián Cabo and Michael C. Georgiadis (2020). "Optimal production scheduling of food process industries." *Computers & Chemical Engineering*, 134, Article number 106682, https://doi.org/10.1016/j.compchemeng.2019.106682

4. Georgios P. Georgiadis, Apostolos P. Elekidis and Michael C. Georgiadis (2021). "Optimal Production Planning and Scheduling in Breweries." *Food and Bioproducts Processing*, 125, 201-221, https://doi.org/10.1016/j.fbp.2020.11.008

5. Georgios P. Georgiadis and Michael C. Georgiadis. Optimal Planning of the COVID-19 Vaccine Supply Chain*. Vaccine*. *Under review*

International conference proceedings

1. Georgios P. Georgiadis, Chrysovalantou Ziogou, Borja Marino Pampin, Daniel Adrian Cabo, Miguel Lopez, Carlos G. Palacin, Cesar de Prada, Carlos Vilas, A. A. Alonso and M. C. Georgiadis (2019). "Optimal Scheduling and Operation of a Food Industrial Plant." *12th European Congress of Chemical Engineering, ECCE12*; September 15-19, Florence, Italy

2. Georgios P. Georgiadis, Chrysovalantou Ziogou, Georgios Kopanos, Marino Pampin, Daniel Cabo, Miguel Lopez, Michael C. Georgiadis (2019). "On the Optimization of Production Scheduling in industrial food Processing Facilities." *Computer-Aided Chemical Engineering*, 46, 793-798

3. Georgios P. Georgiadis, Chrysovalantou Ziogou, Georgios Kopanos, Manuel Garcia, Daniel Cabo, Miguel Lopez, Michael C. Georgiadis (2018). "Production Scheduling of Multi-Stage, Multiproduct Food Process Industries." *Computer-Aided Chemical Engineering*, 43, 1075-1080.

International conference

- Georgios P. Georgiadis, Michael C. Georgiadis (2019). "Scheduling of Food Process Industries." *PSE ASIA, 8th International Symposium of Design, Operation and Control of Chemical Processes*, Bangkok, Thailand, January 13-16

National conference

- Georgios P. Georgiadis, Michael C. Georgiadis (2019). "Optimal Production Scheduling of Food Process Industries." *PSCCE 12, 12th Panhellenic Scientific Conference of Chemical Engineering*, Athens, Greece, May 29-31

Appendices

Appendix A

Data for Illustrative Example (Chapter 2)

Table A.1: Demand used for Approach A

	P1	P2	P3	P4	P5	P6	P7
Monday	211377	1550			123984	112089	252
Tuesday			14061				6578
Wednesday							
Thursday							
Friday		5310		105912			
	P8	**P9**	**P10**	**P11**	**P12**	**P13**	**P14**
Monday	42525		37617	445565			
Tuesday				296097			
Wednesday							
Thursday		32912			61989	90078	
Friday							372420
	P15	**P16**	**P17**	**P18**	**P19**	**P20**	**P21**
Monday	46079	555		267366			32528
Tuesday					51042		
Wednesday					32508	57078	
Thursday			21020	248655			
Friday		2961					
	P22	**P23**	**P24**	**P25**			
Monday							
Tuesday			3428	575486			
Wednesday	38174	5544		285674			
Thursday				488981			
Friday							

Table A.2: Demand used for Approach B

Product	Demand (items)	Due date (hr)	Product	Demand (items)	Due date (hr)
P1	211377	24	**P14**	372420	24
P2	6860	120	**P15**	46079	120
P3	14061	48	**P16**	3516	120
P4	105912	120	**P17**	21020	96
P5	123984	24	**P18**	516021	120
P6	112089	120	**P19**	83550	120
P7	6830	120	**P20**	57078	72
P8	42525	24	**P21**	32528	24

P9	32912	96	**P22**	38174	72
P10	37617	24	**P23**	5544	72
P11	741662	120	**P24**	3428	48
P12	61989	96	**P25**	1350141	120
P13	90078	96			

Table A.3: Processing rate in the continuous lines (items/hr)

	P1	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**P8**	
S1_L1	45128	0	0	45128	45128	0	41026	45128	
S1_L2	45128	45128	30800	45128	45128	41026	0	45128	
S3_L1	0	41026	28000	50400	0	0	40320	0	
S3_L2	50400	0	28000	0	50400	40320	0	42000	
	P9	**P10**	**P11**	**P12**	**P13**	**P14**	**P15**	**P16**	
S1_L1	45128	0	45128	0	45128	45128	45128	0	
S1_L2	45128	45128	45128	45128	45128	0	45128	41026	
S3_L1	0	0	50400	50400	40320	42000	42000	0	
S3_L2	42000	40320	50400	0	0	42000	0	50400	
	P17	**P18**	**P19**	**P20**	**P21**	**P22**	**P23**	**P24**	**P25**
S1_L1	41026	41026	45128	45128	41026	41026	0	45128	45128
S1_L2	0	0	45128	45128	41026	0	45128	0	0
S3_L1	50400	50400	50400	0	0	50400	50400	50400	50400
S3_L2	0	42000	0	42000	42000	42000	0	50400	50400

Table A.4: Data related to the sterilization processing stage

Product	Sterilization time (min)	Sterilizer capacity (items)	Cart capacity (items)
P1	102	29484	3276
P2	98	29484	3276
P3	215	2673	297
P4	168	13770	1530
P5	98	29484	3276
P6	124	22500	2500
P7	124	13770	1530
P8	168	6804	756
P9	98	29484	3276
P10	98	29484	3276
P11	127	13770	1530
P12	98	29484	3276
P13	98	29484	3276
P14	161	6804	756
P15	120	15390	1710
P16	122	29484	3276

P17	98	29484	3276
P18	98	29484	3276
P19	107	29250	3250
P20	162	13770	1530
P21	98	29484	3276
P22	98	29484	3276
P23	98	29484	3276
P24	98	29484	3276
P25	98	29484	3276

Appendix B

Data for the Food Process Industry (Chapter 3)

Case Study I. – Aggregated Approach

Table B.1: Demand (ζ_p) – Case study I

Product	Demand (cans)	Product	Demand (cans)	Product	Demand (cans)
P1	796068	P35	68850	P69	29484
P2	501228	P36	67500	P70	29484
P3	427500	P37	61560	P71	29484
P4	412776	P38	61560	P72	29484
P5	383292	P39	58968	P73	29484
P6	270000	P40	58968	P74	29484
P7	247860	P41	58968	P75	29484
P8	235872	P42	58968	P76	29484
P9	206388	P43	58968	P77	29484
P10	205200	P44	58968	P78	29484
P11	195750	P45	58968	P79	29484
P12	194076	P46	58968	P80	29484
P13	188100	P47	58968	P81	29484
P14	151650	P48	58968	P82	29484
P15	151650	P49	58968	P83	29484
P16	147420	P50	58968	P84	29484
P17	147420	P51	51300	P85	29484
P18	147420	P52	48519	P86	29250
P19	147420	P53	45000	P87	27540
P20	117936	P54	41310	P88	16173
P21	117936	P55	32346	P89	16173
P22	113211	P56	30330	P90	15390
P23	104220	P57	30330	P91	13770
P24	104220	P58	30330	P92	13770

P25	90990	P59	30330	P93	13770
P26	90000	P60	30330	P94	13608
P27	88452	P61	29484	P95	8019
P28	88452	P62	29484	P96	6804
P29	88452	P63	29484	P97	5130
P30	88452	P64	29484	P98	2673
P31	88452	P65	29484	P99	2673
P32	85806	P66	29484	P100	2673
P33	82620	P67	29484	P101	1674
P34	69498	P68	29484	P102	1197

Table B.2: Products p each unit *j* can process for the filling and sealing stage – Case study I

	FS_1	**FS_2**	**FS_3**	**FS_4**	**FS_5**	**FS_6**	**FS_7**	**FS_8**
P1	1	1	1					
P2	1	1	1					
P3					1			
P4	1	1	1					
P5	1	1	1					
P6					1			
P7								1
P8	1	1	1					
P9	1	1	1					
P10							1	
P11					1			
P12					1			
P13							1	
P14	1	1	1					
P15	1	1	1					
P16				1				
P17	1	1	1					
P18	1	1	1					
P19	1	1	1					

P20	1	1	1						
P21				1					
P22									1
P23								1	
P24								1	
P25				1					
P26					1				
P27	1	1	1						
P28	1	1	1						
P29				1					
P30	1	1	1						
P31	1	1	1						
P32						1			
P33									1
P34						1			
P35									1
P36					1				
P37									1
P38					1				
P39	1	1	1						
P40	1	1	1						
P41	1	1	1						
P42	1	1	1						
P43				1					
P44	1	1	1						
P45				1					
P46				1					
P47				1					
P48	1	1	1						
P49	1	1	1						
P50	1	1	1						
P51					1				
P52									1

P53					1			
P54						1		
P55								1
P56				1				
P57				1				
P58				1				
P59				1				
P60				1				
P61				1				
P62	1	1	1					
P63	1	1	1					
P64	1	1	1					
P65	1	1	1					
P66	1	1	1					
P67	1	1	1					
P68	1	1	1					
P69				1				
P70				1				
P71	1	1	1					
P72	1	1	1					
P73	1	1	1					
P74	1	1	1					
P75	1	1	1					
P76	1	1	1					
P77	1	1	1					
P78	1	1	1					
P79	1	1	1					
P80	1	1	1					
P81	1	1	1					
P82	1	1	1					
P83	1	1	1					
P84	1	1	1					
P85	1	1	1					

P86	1	1	1						
P87									1
P88					1				
P89					1				1
P90								1	
P91					1				
P92						1			
P93					1				1
P94						1			
P95						1			
P96						1			
P97						1			
P98						1			
P99						1			
P100						1			
P101						1			
P102						1			

Table B.3: Products p each unit *j* can process in the packing stage – Case study I

	P_1	**P_2**	**P_3**	**P_4**	**P_5**	**P_6**	**P_7**	**P_8**	**P_9**	**P_10**
P1								1		1
P2								1		1
P3		1	1	1						
P4	1					1		1	1	1
P5	1									
P6		1	1							1
P7		1	1	1						1
P8								1		1
P9	1									
P10					1					
P11		1	1	1						
P12		1	1							1

P13					1					
P14	1					1		1	1	1
P15	1					1		1	1	1
P16	1					1				1
P17								1		1
P18								1		1
P19	1					1			1	1
P20		1		1						1
P21	1					1		1	1	1
P22		1	1	1						1
P23				1						1
P24		1		1						1
P25	1					1			1	1
P26		1	1	1						
P27						1				1
P28								1		1
P29	1					1		1	1	1
P30	1					1			1	1
P31	1					1		1	1	1
P32				1			1			1
P33		1	1	1						
P34							1			
P35		1	1	1						
P36		1	1							
P37		1	1	1						1
P38		1	1	1						1
P39	1									
P40								1		1
P41								1		1
P42						1				1
P43	1					1		1	1	1
P44	1							1	1	
P45	1					1		1	1	1

P46	1						1		1	1	1
P47	1						1		1	1	1
P48	1						1			1	1
P49	1						1		1	1	1
P50	1						1		1	1	1
P51		1	1	1							1
P52		1	1	1							
P53		1	1	1							1
P54				1				1			1
P55					1						
P56										1	
P57							1				1
P58	1						1			1	1
P59	1						1		1	1	1
P60	1						1		1	1	1
P61									1		1
P62					1						
P63	1										
P64									1		1
P65									1		1
P66									1		1
P67									1		1
P68									1		1
P69	1						1		1	1	1
P70	1						1		1	1	1
P71	1						1			1	1
P72	1						1			1	1
P73	1						1		1	1	1
P74	1						1		1	1	1
P75	1						1		1	1	1
P76	1						1		1	1	1
P77	1						1		1	1	1
P78	1						1		1	1	1

P79	1					1		1	1	1
P80	1					1		1	1	1
P81	1					1		1	1	1
P82	1					1		1	1	1
P83	1					1		1	1	1
P84	1					1		1	1	1
P85	1					1		1	1	1
P86	1					1		1	1	1
P87		1	1	1						
P88		1	1	1						
P89		1	1	1						
P90		1		1						1
P91					1					
P92				1			1			1
P93		1	1	1						
P94				1			1			1
P95							1			
P96				1			1			1
P97							1			
P98							1			
P99							1			
P100							1			
P101							1			
P102							1			

Table B.4: Processing rate (cans/hour) of product *p* in unit *j* in the filling and sealing stage – Case study I

	FS_1	**FS_2**	**FS_3**	**FS_4**	**FS_5**	**FS_6**	**FS_7**	**FS_8**
P1	24586	22324	23361					
P2	25434	23094	24167					
P3					16824			
P4	27977	25403	26583					
P5	27977	25403	26583					

P6					16824			
P7								14688
P8	27977	25403	26583					
P9	24586	22324	23361					
P10							11569	
P11					16824			
P12					16824			
P13							11569	
P14	27977	25403	26583					
P15	27977	25403	26583					
P16				18574				
P17	24586	22324	23361					
P18	27977	25403	26583					
P19	27977	25403	26583					
P20	27977	25403	26583					
P21				18574				
P22								17626
P23							11569	
P24							11569	
P25				23217				
P26					16824			
P27	27977	25403	26583					
P28	27977	25403	26583					
P29				20895				
P30	27977	25403	26583					
P31	27977	25403	26583					
P32						7078		
P33								14688
P34						3539		
P35								14688
P36					16824			
P37								17626
P38					16824			

P39	24586	22324	23361					
P40	27977	25403	26583					
P41	27977	25403	26583					
P42	27977	25403	26583					
P43				19502				
P44	27977	25403	26583					
P45				20895				
P46				20895				
P47				20895				
P48	27977	25403	26583					
P49	27977	25403	26583					
P50	27977	25403	26583					
P51					15939			
P52								17626
P53					16824			
P54						7078		
P55								17626
P56				23217				
P57				18574				
P58				18574				
P59				18574				
P60				18574				
P61				20895				
P62	27977	25403	26583					
P63	27977	25403	26583					
P64	24586	22324	23361					
P65	27977	25403	26583					
P66	24586	22324	23361					
P67	24586	22324	23361					
P68	27977	25403	26583					
P69				18574				
P70				19502				
P71	27977	25403	26583					

P72	27977	25403	26583					
P73	27977	25403	26583					
P74	27977	25403	26583					
P75	27977	25403	26583					
P76	27977	25403	26583					
P77	27977	25403	26583					
P78	27977	25403	26583					
P79	27977	25403	26583					
P80	27977	25403	26583					
P81	25434	25403	26583					
P82	27977	25403	26583					
P83	27977	25403	26583					
P84	27977	25403	26583					
P85	27977	25403	26583					
P86	27977	25403	26583					
P87								17626
P88				16824				
P89				18595				15422
P90						11569		
P91				16824				
P92					7078			
P93				17710				14688
P94					7078			
P95					3539			
P96					7078			
P97					1769			
P98					3539			
P99					3539			
P100					3539			
P101					1769			
P102					1769			

Table B.5: Processing rate (cans/hour) of product *p* in unit *j* in the packing stage – Case study I

	P_1	P_2	P_3	P_4	P_5	P_6	P_7	P_8	P_9	P_10
P1								46476		30947
P2								46476		30947
P3		12684	13552	13557						
P4	22964					24862		31371	19296	20632
P5	22964									
P6		16021	17119							14786
P7		16021	17119	17124						14786
P8								46476		30947
P9	22964									
P10					7693					
P11		16021	17119	17124						
P12		12684	13552							16505
P13					7693					
P14	22964					24862		31371	19296	20632
P15	22964					24862		31371	19296	20632
P16	19137					20718				20632
P17								46476		30947
P18								46476		30947
P19	19137					20718			19296	20632
P20		20027		21406						20632
P21	22964					24862		31371	19296	20632
P22		16021	17119	17124						17193
P23				13557						16505
P24		16021		13557						14786
P25	19137					20718			19296	20632
P26		16021	17119	17124						
P27						27348				20632
P28								46476		30947
P29	22964					24862		31371	19296	20632
P30	18372					24862			15437	16505
P31	22964					24862		31371	19296	20632
P32				9989			7335			8597
P33		16021	17119	17124						

P34							1956			
P35		16021	17119	17124						
P36		16021	17119							
P37		16021	17119	17124						17193
P38		16021	17119	17124						17193
P39	22964									
P40								46476		30947
P41								46476		30947
P42						27348				20632
P43	22964					24862		31371	19296	20632
P44	15310							31371	14472	
P45	22964					24862		31371	19296	20632
P46	22964					24862		31371	19296	20632
P47	22964					24862		31371	19296	20632
P48	22964					24862			19296	20632
P49	22964					24862		31371	19296	20632
P50	22964					24862		31371	19296	20632
P51		16021	17119	17124						24070
P52		12684	13552	13557						
P53		16021	17119	17124						14786
P54				9989			7335			8597
P55					10551					
P56									19296	
P57						27348				20632
P58	18372					19889			15437	16505
P59	22964					24862		31371	19296	20632
P60	22964					24862		31371	19296	20632
P61								46476		30947
P62					10991					
P63	22964									
P64								46476		30947
P65								46476		30947
P66								46476		30947
P67								46476		30947
P68								46476		30947
P69	22964					24862		31371	19296	20632

P70	22964					24862		31371	19296	20632
P71	18372					19889			15437	16505
P72	22964					24862			19296	20632
P73	22964					24862		31371	19296	20632
P74	22964					24862		31371	19296	20632
P75	22964					24862		31371	19296	20632
P76	22964					24862		31371	19296	20632
P77	22964					24862		31371	19296	20632
P78	22964					24862		31371	19296	20632
P79	22964					24862		31371	19296	20632
P80	22964					24862		31371	19296	20632
P81	22964					24862		31371	19296	20632
P82	22964					24862		31371	19296	20632
P83	22964					24862		31371	19296	20632
P84	22964					24862		31371	19296	20632
P85	22964					24862		31371	19296	20632
P86	22964					24862		31371	19296	20632
P87		16021	17119	17124						
P88		12684	13552	13557						
P89		12684	13552	13557						
P90		3338		7421						14328
P91					7913					
P92				8562			7335			8597
P93		16021	17119	17124						
P94				9989			7335			8597
P95							2347			
P96				9989			7335			8597
P97							1956			
P98							2347			
P99							2934			
P100							2347			
P101							1956			
P102							1956			

Table B.6: Number of sterilizers used by each product – Case study I

Product	κ_P	Product	κ_P	Product	κ_P
P1	1	P35	2	P69	2
P2	1	P36	1	P70	2
P3	1	P37	2	P71	1
P4	1	P38	2	P72	1
P5	1	P39	1	P73	1
P6	1	P40	1	P74	1
P7	2	P41	1	P75	1
P8	1	P42	1	P76	1
P9	1	P43	2	P77	1
P10	1	P44	1	P78	1
P11	2	P45	2	P79	1
P12	1	P46	2	P80	1
P13	1	P47	2	P81	1
P14	1	P48	1	P82	1
P15	1	P49	1	P83	1
P16	1	P50	1	P84	1
P17	1	P51	2	P85	1
P18	1	P52	1	P86	1
P19	1	P53	1	P87	2
P20	1	P54	2	P88	1
P21	2	P55	1	P89	1
P22	2	P56	1	P90	1
P23	2	P57	2	P91	1
P24	2	P58	2	P92	2
P25	1	P59	2	P93	2
P26	1	P60	2	P94	3
P27	1	P61	2	P95	2
P28	1	P62	1	P96	3
P29	2	P63	1	P97	1
P30	1	P64	1	P98	2
P31	1	P65	1	P99	2
P32	3	P66	1	P100	2

P33	2	P67	1	P101	3
P34	2	P68	1	P102	4

Table B.7: Required sterilization time for product p – Case study I

Product	Batch time (min)	Product	Batch time (min)	Product	Batch time (min)
P1	82	P35	106	P69	82
P2	85	P36	85	P70	82
P3	85	P37	100	P71	82
P4	82	P38	98	P72	82
P5	82	P39	82	P73	82
P6	85	P40	82	P74	82
P7	103	P41	82	P75	102
P8	82	P42	82	P76	82
P9	82	P43	82	P77	82
P10	115	P44	82	P78	82
P11	120	P45	82	P79	82
P12	85	P46	82	P80	82
P13	115	P47	82	P81	82
P14	85	P48	82	P82	82
P15	85	P49	82	P83	102
P16	102	P50	82	P84	82
P17	82	P51	94	P85	82
P18	82	P52	85	P86	82
P19	82	P53	85	P87	106
P20	82	P54	135	P88	85
P21	82	P55	85	P89	98
P22	85	P56	85	P90	120
P23	85	P57	82	P91	106
P24	120	P58	85	P92	135
P25	85	P59	82	P93	106
P26	85	P60	82	P94	140
P27	82	P61	82	P95	179

P28	82	P62	82	P96	140
P29	82	P63	82	P97	85
P30	102	P64	82	P98	179
P31	82	P65	82	P99	179
P32	135	P66	82	P100	179
P33	106	P67	82	P101	286
P34	179	P68	82	P102	271

Table B.8: Cart capacity for product *p* – Case study I

Product	**Capacity (cans)**	**Product**	**Capacity (cans)**	**Product**	**Capacity (cans)**
P1	3276	P35	1530	P69	3276
P2	3276	P36	2500	P70	3276
P3	2500	P37	1710	P71	3276
P4	3276	P38	1710	P72	3276
P5	3276	P39	3276	P73	3276
P6	2500	P40	3276	P74	3276
P7	1530	P41	3276	P75	3276
P8	3276	P42	3276	P76	3276
P9	3276	P43	3276	P77	3276
P10	1900	P44	3276	P78	3276
P11	1450	P45	3276	P79	3276
P12	1797	P46	3276	P80	3276
P13	1900	P47	3276	P81	3276
P14	3370	P48	3276	P82	3276
P15	3370	P49	3276	P83	3276
P16	3276	P50	3276	P84	3276
P17	3276	P51	1900	P85	3276
P18	3276	P52	1797	P86	3250
P19	3276	P53	2500	P87	1530
P20	3276	P54	1530	P88	1797
P21	3276	P55	1797	P89	1797
P22	1797	P56	3370	P90	1710

P23	1930	P57	3370	P91	1530
P24	1930	P58	3370	P92	1530
P25	3370	P59	3370	P93	1530
P26	2500	P60	3370	P94	756
P27	3276	P61	3276	P95	297
P28	3276	P62	3276	P96	756
P29	3276	P63	3276	P97	190
P30	3276	P64	3276	P98	297
P31	3276	P65	3276	P99	297
P32	681	P66	3276	P100	297
P33	1530	P67	3276	P101	186
P34	297	P68	3276	P102	133

Table B.9: Demand – Case study II

Product	**Demand (cans)**	**Due (hr)**	**Product**	**Demand (cans)**	**Due (hr)**
P1	762120	148	P64	40000	148
P2	762120	148	P65	40000	148
P3	762120	148	P66	40000	148
P4	750000	148	P67	40000	148
P5	528780	148	P68	40000	148
P6	500000	148	P69	35000	148
P7	500000	24	P70	35000	148
P8	460000	148	P71	30000	148
P9	457920	148	P72	30000	148
P10	457920	148	P73	30000	148
P11	300000	148	P74	30000	148
P12	279936	148	P75	30000	148
P13	250000	148	P76	30000	148
P14	200000	148	P77	30000	148
P15	200000	148	P78	30000	24
P16	200000	148	P79	30000	148
P17	150000	148	P80	30000	148
P18	150000	148	P81	30000	148
P19	150000	148	P82	30000	148
P20	130000	148	P83	30000	148
P21	120000	148	P84	30000	148
P22	120000	148	P85	30000	148

P23	115000	24	P86	30000	148
P24	107136	148	P87	30000	148
P25	101088	148	P88	26000	148
P26	100000	148	P89	25000	148
P27	100000	148	P90	25000	24
P28	100000	148	P91	22000	148
P29	100000	148	P92	20000	148
P30	100000	148	P93	20000	148
P31	100000	148	P94	20000	148
P32	100000	148	P95	20000	148
P33	100000	148	P96	20000	148
P34	100000	148	P97	20000	24
P35	93312	148	P98	20000	148
P36	93312	148	P99	20000	148
P37	90000	148	P100	20000	148
P38	90000	148	P101	15000	148
P39	87696	24	P102	15000	148
P40	86000	148	P103	15000	148
P41	80000	148	P104	15000	148
P42	80000	148	P105	15000	148
P43	70000	148	P106	15000	148
P44	70000	148	P107	15000	24
P45	60000	148	P108	15000	148
P46	60000	148	P109	13000	148
P47	60000	148	P110	10000	148
P48	60000	148	P111	10000	148
P49	60000	148	P112	10000	148
P50	60000	148	P113	10000	24
P51	60000	148	P114	10000	148
P52	60000	96	P115	10000	148
P53	60000	148	P116	8000	148
P54	60000	148	P117	6000	148
P55	60000	148	P118	6000	148
P56	50000	148	P119	5000	148
P57	50000	148	P120	5000	148
P58	50000	148	P121	5000	148
P59	50000	148	P122	5000	148
P60	50000	148	P123	3500	148
P61	50000	148	P124	3000	148
P62	50000	148	P125	3000	148
P63	43200	148	P126	2000	148

Table B.10: Products *p* each unit *j* can process for the filling and sealing stage– Case study II

	FS_1	FS_2	FS_3	FS_4	FS_5	FS_6	FS_7	FS_8
P1	1	1	1					
P2	1	1	1					
P3	1	1	1					
P4	1	1	1					
P5					1			
P6	1	1	1					
P7	1	1	1					
P8				1				
P9								1
P10								1
P11					1			
P12								1
P13	1	1	1	1				
P14	1	1	1					
P15							1	
P16	1	1	1					
P17							1	
P18								1
P19				1				
P20					1			
P21	1	1	1	1				
P22	1	1	1					
P23	1	1	1					
P24					1			
P25					1			
P26	1	1	1					
P27					1			1
P28	1	1	1					
P29							1	
P30								1
P31	1	1	1					
P32	1	1	1					
P33	1	1	1					
P34							1	
P35					1			
P36								1
P37	1	1	1	1				
P38							1	
P39					1			

P40				1					
P41				1					
P42	1	1	1						
P43	1	1	1						
P44	1	1	1						
P45					1				
P46									1
P47	1	1	1						
P48									1
P49				1					
P50	1	1	1						
P51	1	1	1						
P52				1					
P53				1					
P54	1	1	1	1					
P55							1		
P56	1	1	1						
P57					1				1
P58				1					
P59	1	1	1						
P60	1	1	1						
P61				1					
P62						1			
P63						1			
P64	1	1	1						
P65	1	1	1						
P66					1				1
P67				1					
P68				1					
P69	1	1	1						
P70	1	1	1	1					
P71	1	1	1	1					
P72	1	1	1						
P73	1	1	1						
P74					1				1
P75				1					
P76	1	1	1						
P77									1
P78	1	1	1						
P79				1					
P80				1					
P81	1	1	1						
P82	1	1	1						

P83				1					
P84						1			
P85									1
P86	1	1	1						
P87							1		
P88	1	1	1						
P89	1	1	1						
P90	1	1	1						
P91				1					
P92									1
P93					1				1
P94					1				
P95				1					
P96	1	1	1						
P97						1			
P98							1		
P99						1			
P100						1			
P101				1					
P102	1	1	1						
P103	1	1	1						
P104					1				
P105									1
P106					1				
P107	1	1	1						
P108									1
P109						1			
P110					1				
P111									1
P112									1
P113						1			
P114						1			
P115						1			
P116						1			
P117						1			
P118						1			
P119						1			
P120					1				
P121						1			
P122						1			
P123						1			
P124						1			
P125						1			

P126							1			

Table B.11: Products *p* each unit *j* can process for the packing stage– Case study II

	P_1	**P_2**	**P_3**	**P_4**	**P_5**	**P_6**	**P_7**	**P_8**	**P_9**	**P_10**
P1	1					1		1	1	1
P2	1					1		1	1	1
P3	1					1		1	1	1
P4						1				1
P5					1					
P6	1									
P7								1		1
P8	1					1		1	1	1
P9		1	1							
P10		1	1							
P11					1					
P12		1	1							
P13	1					1			1	1
P14		1		1						1
P15									1	
P16								1		1
P17		1	1	1						1
P18		1	1	1						1
P19								1		1
P20		1	1							
P21	1					1		1	1	1
P22								1		1
P23		1		1						1
P24					1					
P25		1	1	1						1
P26	1									
P27					1					
P28						1				1
P29		1	1							
P30		1	1	1						1
P31	1					1		1	1	1
P32								1		1
P33								1		1
P34				1			1			1
P35					1					
P36		1	1	1						
P37								1		1
P38				1			1			1

P39					1					
P40	1					1				1
P41	1					1		1	1	1
P42	1					1		1	1	1
P43	1					1		1	1	1
P44	1					1		1	1	1
P45					1					
P46		1	1							1
P47	1					1			1	1
P48		1	1	1						1
P49	1					1		1	1	1
P50	1					1		1	1	1
P51	1					1		1	1	1
P52										1
P53								1		1
P54								1		1
P55				1			1			1
P56	1							1	1	
P57		1	1	1						1
P58	1					1		1	1	1
P59	1					1		1	1	1
P60								1		1
P61								1		1
P62				1			1			1
P63				1			1			
P64	1									
P65		1		1						1
P66		1	1	1						1
P67	1					1		1	1	1
P68				1						1
P69	1					1		1	1	1
P70									1	1
P71	1									
P72					1					
P73	1								1	
P74		1	1	1						
P75	1					1			1	
P76	1					1		1		
P77		1	1	1						1
P78	1					1		1	1	1
P79	1					1		1	1	1
P80	1					1		1	1	1
P81	1					1		1	1	1

P82	1						1		1	1	1
P83	1						1		1	1	1
P84								1			
P85										1	
P86									1	1	
P87				1							1
P88	1						1		1	1	1
P89	1						1				1
P90										1	
P91	1						1			1	1
P92					1						
P93		1	1	1							
P94		1	1	1							1
P95	1						1			1	1
P96	1						1		1	1	1
P97								1			
P98				1				1			1
P99				1				1			1
P100				1				1			1
P101							1				
P102	1						1		1		
P103	1						1				1
P104		1	1	1							1
P105		1	1	1							1
P106		1	1	1							1
P107										1	
P108										1	
P109				1				1			
P110		1		1							1
P111		1	1	1							1
P112		1	1	1							1
P113								1			
P114								1			
P115				1				1			1
P116				1				1			
P117				1				1			
P118				1				1			1
P119					1						
P120		1									1
P121								1			
P122								1			1
P123				1				1			1
P124								1			

P125	1	1	1
P126		1	

Table B.12: Processing rate (cans/hour) of product *p* in unit *j* in the filling and sealing stage - Case study II

	FS_1	FS_2	FS_3	FS_4	FS_5	FS_6	FS_7	FS_8
P1	27978	25404	26584					
P2	27978	25404	26584					
P3	27978	25404	26584					
P4	27978	25404	26584					
P5					16825			
P6	24587	22325	23362					
P7	25434	23094	24167					
P8				18574				
P9								17626
P10								17626
P11					16825			
P12								17626
P13	27978	25404	26584	23217				
P14	27978	25404	26584					
P15							7713	
P16	27978	25404	26584					
P17							11569	
P18	27978	25404	26584					
P19				20896				
P20					16825			
P21	27978	25404	26584	23217				
P22	27978	25404	26584					
P23	27978	25404	26584					
P24					16825			
P25					16825			
P26	27978	25404	26584					
P27					16825			14688
P28	27978	25404	26584					
P29							11569	
P30								17626
P31	27978	25404	26584					
P32	24587	22325	23362					
P33	27978	25404	26584					
P34							7713	
P35					16825			
P36								17626

P37	27978	25404	26584	23217				
P38							7713	
P39					16825			
P40				18574				
P41				20896				
P42	27978	25404	26584					
P43	27978	25404	26584					
P44								14688
P45					16825			
P46								14688
P47	27978	25404	26584					
P48								17626
P49				19503				
P50	27978	25404	26584					
P51	27978	25404	26584					
P52				20896				
P53				19503				
P54	27978	25404	26584	23217				
P55							8484	
P56	27978	25404	26584					
P57					16825			14688
P58				20896				
P59	25434	25404	26584					
P60	24587	22325	23362					
P61				20896				
P62						7078		
P63						7078		
P64	27978	25404	26584					
P65	27978	25404	26584					
P66					16825			14688
P67				20896				
P68				18574				
P69	27978	25404	26584					
P70	27978	25404	26584	23217				
P71	27978	25404	26584	25539				
P72	27978	25404	26584					
P73	27978	25404	26584					
P74					16825			14688
P75				23217				
P76	27978	25404	26584					
P77								13954
P78	27978	25404	26584					
P79				20896				

P80				18574				
P81	27978	25404	26584					
P82	27978	25404	26584					
P83				20896				
P84						3539		
P85								17626
P86	27978	25404	26584					
P87							7713	
P88	27978	25404	26584					
P89	27978	25404	26584					
P90	27978	25404	26584					
P91				20896				
P92								17626
P93					18596			17626
P94					16825			
P95				18574				
P96	27978	25404	26584					
P97						7078		
P98							7713	
P99						7078		
P100						7078		
P101				20896				
P102	27978	25404	26584					
P103	27978	25404	26584					
P104					18596			
P105								17626
P106					18596			
P107	27978	25404	26584					
P108								17626
P109						7078		
P110					18596			
P111								17626
P112								17626
P113						7078		
P114						7078		
P115						7078		
P116						3539		
P117						3539		
P118						7078		
P119						7078		
P120					16825			
P121						3539		
P122						3539		

P123	3539
P124	3539
P125	7078
P126	3539

Table B.13: Processing rate (cans/hour) of product *p* in unit *j* in the packing stage – Case study II

	P_1	P_2	P_3	P_4	P_5	P_6	P_7	P_8	P_9	P_10
P1	22965					24862		31372	19296	20632
P2	22965					24862		31372	19296	20632
P3	22965					24862		31372	19296	20632
P4						27348				20632
P5					10551					
P6	22965									
P7								46476		30948
P8	22965					24862		31372	19296	20632
P9		16022	17119							
P10		16022	17119							
P11					10551					
P12		16022	17119							
P13	19137					20718			19296	20632
P14		20027		21406						20632
P15									15437	
P16								46476		30948
P17		16022	17119	17125						17193
P18	22965					24862		31372	19296	20632
P19								46476		30948
P20		12684	13553							
P21	22965					24862		31372	19296	20632
P22								46476		30948
P23		20027		21406						20632
P24					10551					
P25		12684	13553	13557						16506
P26	22965									
P27					7210					
P28						27348				20632
P29		12684	13553							
P30		16022	17119	17125						16506
P31	22965					24862		31372	19296	20632
P32								46476		30948
P33								46476		30948
P34				8563			7335			8597
P35					10551					
P36		16022	17119	17125						
P37								46476		30948

P38				9990			7335			8597
P39					8793					
P40	19137					20718				20632
P41	22965					24862		31372	19296	20632
P42	22965					24862		31372	19296	20632
P43	22965					24862		31372	19296	20632
P44		16022	17119	17125						14786
P45					6595					
P46		16022	17119							14786
P47	18372					19890			15437	16506
P48		16022	17119	17125						17193
P49	22965					24862		31372	19296	20632
P50	22965					24862		31372	19296	20632
P51	22965					24862		31372	19296	20632
P52										30948
P53								46476		30948
P54								46476		30948
P55				9990			7335			8597
P56	15310							31372	14472	
P57		16022	17119	17125						14786
P58	22965					24862		31372	19296	20632
P59	22965					24862		31372	19296	20632
P60								46476		30948
P61								46476		30948
P62				4282			2934			8597
P63				4710			4303			
P64	22965									
P65		16689		17838						29229
P66		16022	17119	17125						14786
P67	22965					24862		31372	19296	20632
P68				21406						20632
P69	22965					24862		31372	19296	20632
P70									4342	30948
P71	22965									
P72					10991					
P73	7655								9648	
P74		16022	17119	17125						
P75	22965					24862			19296	
P76	22965					24862		31372		
P77		9346	9986	7421						14328
P78	22965					24862		31372	19296	20632
P79	22965					24862		31372	19296	20632
P80	22965					24862		31372	19296	20632
P81	22965					24862		31372	19296	20632
P82	22965					24862		31372	19296	20632
P83	22965					24862		31372	19296	20632

P84							1956			
P85									8040	
P86								31372	19296	
P87				13557						24071
P88	22965					24862		31372	19296	20632
P89	19137					20718				20632
P90									19296	
P91	22965					24862			19296	20632
P92					6595					
P93		12684	13553	13557						
P94		16022	17119	17125						17193
P95	18372					19890			15437	16506
P96	22965					24862		31372	19296	20632
P97							7335			
P98				4710			4303			4539
P99				9990			7335			8597
P100				9990			7335			8597
P101						27348				
P102	22965					24862		31372		
P103	19137					20718				20632
P104		12684	13553	13557						13205
P105		16022	17119	17125						17193
P106		12684	13553	13557						13205
P107									19296	
P108									8040	
P109				9990			7335			
P110		3338		7421						14328
P111		8345	13553	8563						17193
P112		16022	17119	17125						14786
P113							7335			
P114							7335			
P115				9990			7335			8597
P116				4282			2934			
P117				4282			2348			
P118				9990			7335			8597
P119					5276					
P120		3338								14328
P121							1630			
P122							3912			4952
P123				4282			3912			4952
P124							3912			
P125				9990			7335			8597
P126							1956			

Table B.14: Number of sterilizers used by each product p – Case study II

Product	κ_P	Product	κ_P	Product	κ_P
P1	2	P43	2	P85	2
P2	2	P44	2	P86	1
P3	2	P45	2	P87	2
P4	2	P46	2	P88	1
P5	2	P47	2	P89	1
P6	2	P48	2	P90	1
P7	3	P49	2	P91	1
P8	2	P50	2	P92	2
P9	2	P51	2	P93	2
P10	2	P52	2	P94	2
P11	2	P53	3	P95	1
P12	1	P54	3	P96	1
P13	2	P55	5	P97	3
P14	2	P56	2	P98	2
P15	3	P57	3	P99	2
P16	3	P58	2	P100	4
P17	3	P59	2	P101	1
P18	3	P60	2	P102	1
P19	3	P61	2	P103	1
P20	2	P62	5	P104	1
P21	2	P63	1	P105	1
P22	3	P64	2	P106	1
P23	2	P65	2	P107	1
P24	2	P66	2	P108	1
P25	2	P67	2	P109	1
P26	2	P68	2	P110	1
P27	2	P69	2	P111	1
P28	2	P70	2	P112	1
P29	2	P71	1	P113	1
P30	2	P72	2	P114	2
P31	2	P73	2	P115	2
P32	3	P74	2	P116	3
P33	3	P75	1	P117	3
P34	2	P76	1	P118	1
P35	2	P77	2	P119	1
P36	2	P78	2	P120	1
P37	3	P79	2	P121	2
P38	2	P80	2	P122	2
P39	1	P81	2	P123	2
P40	2	P82	2	P124	1

P41	2	P83	2	P125	1
P42	2	P84	4	P126	1

Table B.15: Required sterilization time for product p – Case study II

Product	Batch time (min)	Product	Batch time (min)	Product	Batch time (min)
P1	82	P43	85	P85	100
P2	82	P44	82	P86	85
P3	82	P45	98	P87	120
P4	82	P46	100	P88	82
P5	98	P47	82	P89	82
P6	82	P48	98	P90	82
P7	85	P49	82	P91	82
P8	82	P50	82	P92	98
P9	103	P51	105	P93	98
P10	103	P52	82	P94	98
P11	98	P53	82	P95	85
P12	82	P54	82	P96	82
P13	82	P55	221	P97	135
P14	82	P56	82	P98	221
P15	120	P57	103	P99	135
P16	82	P58	85	P100	135
P17	120	P59	82	P101	82
P18	103	P60	82	P102	82
P19	82	P61	82	P103	82
P20	98	P62	168	P104	100
P21	82	P63	135	P105	100
P22	82	P64	82	P106	100
P23	82	P65	82	P107	82
P24	98	P66	103	P108	100
P25	98	P67	82	P109	140
P26	85	P68	102	P110	100
P27	120	P69	102	P111	113
P28	82	P70	82	P112	100
P29	120	P71	82	P113	140
P30	100	P72	89	P114	135
P31	85	P73	82	P115	146
P32	82	P74	106	P116	179
P33	85	P75	85	P117	180
P34	140	P76	105	P118	140
P35	120	P77	120	P119	134
P36	106	P78	82	P120	100

P37	82	P79	82	P121	168
P38	160	P80	82	P122	179
P39	82	P81	82	P123	213
P40	102	P82	82	P124	179
P41	82	P83	82	P125	146
P42	85	P84	179	P126	180

Table B.16: Cart capacity for product p – Case study II

Product	**Capacity (cans)**	**Product**	**Capacity (cans)**	**Product**	**Capacity (cans)**
P1	372	P43	3276	P85	3276
P2	372	P44	1530	P86	1797
P3	372	P45	1797	P87	2500
P4	3276	P46	3276	P88	3276
P5	1797	P47	3276	P89	3276
P6	756	P48	3370	P90	1797
P7	3276	P49	3276	P91	1530
P8	3276	P50	1530	P92	3370
P9	3370	P51	297	P93	3276
P10	3370	P52	3276	P94	3250
P11	2500	P53	3276	P95	3370
P12	1797	P54	3276	P96	3250
P13	1710	P55	3276	P97	2500
P14	3276	P56	3276	P98	3276
P15	2500	P57	3276	P99	1710
P16	3276	P58	756	P100	1710
P17	3276	P59	3276	P101	3370
P18	2500	P60	3276	P102	3276
P19	3276	P61	756	P103	1530
P20	1797	P62	1797	P104	3276
P21	3276	P63	3276	P105	1710
P22	1710	P64	3370	P106	3276
P23	3276	P65	756	P107	1530
P24	3370	P66	3276	P108	3276
P25	1797	P67	3276	P109	297
P26	1930	P68	1530	P110	756
P27	297	P69	1530	P111	1797
P28	3276	P70	1797	P112	1710
P29	1530	P71	3370	P113	681
P30	756	P72	1530	P114	3276
P31	3370	P73	1530	P115	372
P32	3276	P74	3276	P116	3276

P33	372	P75	3276	P117	297
P34	1530	P76	3370	P118	1530
P35	3370	P77	1530	P119	3276
P36	1797	P78	3276	P120	1530
P37	3276	P79	3276	P121	3276
P38	1930	P80	1710	P122	1530
P39	320	P81	3276	P123	3276
P40	756	P82	1797	P124	3370
P41	433	P83	1514	P125	3276
P42	3276	P84	3276	P126	1797

Appendix C

Data for the COVID-19 Vaccine Supply Chain Problem (Chapter 5)

Table C.1: Illustrative example – Vaccination centre's data

Vaccination centre	Vaccination goal (ζ_{vc})	Maximum number of healthcare workers (ι_{vc}^{max})	Base number of healthcare workers (ι_{vc}^{b})	Maximum storage (θ_{vc})	Initial storage ($\alpha_{vc,v}$)	
					P	M
C1	10452	54	37	528	88	88
C2	9780	51	34	492	82	82
C3	6300	33	22	324	54	54
C4	3168	17	11	168	28	28
C5	1440	8	5	72	12	12

Table C.2: Illustrative Example – Hub's data

Hub	Initial Storage ($\alpha_{h,v}$)		Maximum storage ($\gamma_{h,c}$)	
	P	M	Freezer (M)	Deep freezer (P)
H	260	260	1300	1300

Table C.3: Illustrative example – Vaccines' data

Vaccine	Maximum supply ($\pi_{h,v}^{max}$)	Minimum flow from hub to centres ($\rho_{f,h}^{min}$)	Doses per vial (δ_v)	Cost ξ_v (RMU)	Shelf-life λ_v (days)
P	3000	975	6	12	5
M	2000	100	10	18	-

Table C.4: Illustrative example – Distance matrix

Distance $\mu_{h,vc}$ (km)					
	C1	**C2**	**C3**	**C4**	**C5**
H	114	15	193	96	45

Table C.5: Illustrative example - Cost data A

Healthcare personnel cost (RMU†/day)	**Truck rental cost (RMU)**	**Storage technology cost (RMU/day/via)**		
		Refrigerator	**Freezer**	**Deep freezer**
120	270	0.5	1.5	3

Table C.6: Illustrative example - Cost data B

Fuel consumption (lt/100km)	**Fuel price (RMU/lt)**	**Average truck speed (km/h)**	**Driver's wage (RMU/hour)**
10	1.3	50	8

† Relative Monetary Units

Table C.7: Greek Case study – Connectivity between hubs and vaccination centres

Hub	VC	Hub	VC	Hub	VC	Hub	VC	Hub	VC	Hub	VC	Hub	VC
H1	C082	H1	C148	H1	C198	H2	C269	H3	C249	H4	C002	H4	C052
H1	C083	H1	C149	H1	C199	H2	C270	H3	C250	H4	C003	H4	C053
H1	C084	H1	C150	H1	C200	H2	C271	H3	C251	H4	C004	H4	C054
H1	C085	H1	C151	H1	C201	H2	C272	H3	C252	H4	C005	H4	C055
H1	C086	H1	C152	H1	C202	H2	C273	H3	C256	H4	C006	H4	C056
H1	C087	H1	C153	H1	C203	H2	C279	H3	C257	H4	C007	H4	C057
H1	C088	H1	C154	H2	C091	H2	C280	H3	C258	H4	C008	H4	C059
H1	C089	H1	C155	H2	C092	H2	C281	H3	C260	H4	C009	H4	C061
H1	C090	H1	C156	H2	C093	H2	C282	H3	C261	H4	C010	H4	C062
H1	C096	H1	C157	H2	C094	H2	C283	H3	C262	H4	C011	H4	C063
H1	C097	H1	C158	H2	C095	H2	C284	H3	C263	H4	C012	H4	C064
H1	C098	H1	C159	H2	C118	H2	C285	H3	C264	H4	C013	H4	C065
H1	C099	H1	C160	H2	C119	H2	C286	H3	C265	H4	C014	H4	C066
H1	C100	H1	C161	H2	C120	H2	C287	H3	C266	H4	C015	H4	C067
H1	C101	H1	C162	H2	C121	H2	C288	H3	C267	H4	C016	H4	C068
H1	C102	H1	C163	H2	C122	H2	C289	H3	C274	H4	C017	H4	C069
H1	C103	H1	C164	H2	C134	H2	C290	H3	C275	H4	C018	H4	C070
H1	C104	H1	C165	H2	C135	H2	C291	H3	C276	H4	C019	H4	C071
H1	C105	H1	C166	H2	C136	H2	C292	H3	C277	H4	C020	H4	C072
H1	C106	H1	C167	H2	C137	H2	C293	H3	C278	H4	C021	H4	C073
H1	C107	H1	C168	H2	C138	H2	C294	H3	C299	H4	C022	H4	C074
H1	C108	H1	C169	H2	C139	H2	C295	H3	C300	H4	C023	H4	C075
H1	C109	H1	C170	H2	C204	H2	C296	H3	C301	H4	C024	H4	C076
H1	C110	H1	C171	H2	C205	H2	C297	H3	C302	H4	C025	H4	C077
H1	C111	H1	C172	H2	C206	H2	C298	H3	C303	H4	C026	H4	C078

H1	C112	H1	C173	H2	C207	H2	C328	H3	C304	H4	C027	H4	C079
H1	C113	H1	C174	H2	C208	H2	C329	H3	C305	H4	C028	H4	C080
H1	C114	H1	C175	H2	C214	H3	C060	H3	C306	H4	C029	H4	C081
H1	C115	H1	C176	H2	C217	H3	C209	H3	C307	H4	C030	H5	C330
H1	C116	H1	C177	H2	C218	H3	C210	H3	C308	H4	C031	H5	C331
H1	C117	H1	C178	H2	C219	H3	C211	H3	C309	H4	C032	H5	C332
H1	C123	H1	C179	H2	C220	H3	C212	H3	C310	H4	C033	H5	C333
H1	C124	H1	C180	H2	C221	H3	C213	H3	C311	H4	C034	H5	C334
H1	C125	H1	C181	H2	C222	H3	C215	H3	C312	H4	C035	H5	C335
H1	C126	H1	C182	H2	C223	H3	C216	H3	C313	H4	C036	H5	C336
H1	C127	H1	C183	H2	C224	H3	C234	H3	C314	H4	C037	H5	C337
H1	C128	H1	C184	H2	C225	H3	C235	H3	C315	H4	C038	H5	C338
H1	C129	H1	C185	H2	C226	H3	C236	H3	C316	H4	C039	H5	C339
H1	C130	H1	C186	H2	C227	H3	C237	H3	C317	H4	C040	H5	C340
H1	C131	H1	C187	H2	C228	H3	C238	H3	C318	H4	C041	H5	C341
H1	C132	H1	C188	H2	C229	H3	C239	H3	C319	H4	C042	H5	C342
H1	C133	H1	C189	H2	C230	H3	C240	H3	C320	H4	C043	H5	C343
H1	C140	H1	C190	H2	C231	H3	C241	H3	C321	H4	C044	H5	C344
H1	C141	H1	C191	H2	C232	H3	C242	H3	C322	H4	C045	H5	C345
H1	C142	H1	C192	H2	C233	H3	C243	H3	C323	H4	C046	H5	C346
H1	C143	H1	C193	H2	C253	H3	C244	H3	C324	H4	C047	H5	C347
H1	C144	H1	C194	H2	C254	H3	C245	H3	C325	H4	C048	H5	C348
H1	C145	H1	C195	H2	C255	H3	C246	H3	C326	H4	C049	H5	C349
H1	C146	H1	C196	H2	C259	H3	C247	H3	C327	H4	C050	H5	C350
H1	C147	H1	C197	H2	C268	H3	C248	H4	C001	H4	C051	H5	C351

Table C.8: Greek Case study - Distribution of vaccination centres into clusters

VC	Cluster	VC	Cluster	VC	Cluster	VC	Cluster	VC	Cluster	VC	Cluster	VC	Cluster
C001	CLU25b	C051	CLU02	C102	CLU20a	C152	CLU42	C202	CLU13	C252	CLU14	C302	CLU28
C002	CLU25b	C052	CLU25a	C103	CLU20a	C153	CLU13	C203	CLU13	C253	CLU30	C303	CLU28
C003	CLU25b	C053	CLU11	C104	CLU20b	C154	CLU13	C204	CLU23	C254	CLU15	C304	CLU28
C004	CLU25b	C054	CLU37	C105	CLU20b	C155	CLU20d	C205	CLU30	C255	CLU15	C305	CLU06
C005	CLU25a	C055	CLU37	C106	CLU20b	C156	CLU20d	C206	CLU30	C256	CLU48	C306	CLU28
C006	CLU25b	C056	CLU35	C107	CLU20c	C157	CLU20d	C207	CLU33	C257	CLU48	C307	CLU06
C007	CLU25b	C057	CLU37	C108	CLU20c	C158	CLU20d	C208	CLU45	C258	CLU48	C308	CLU06
C008	CLU25a	C059	CLU02	C109	CLU20d	C159	CLU49	C209	CLU07	C259	CLU32	C309	CLU16
C009	CLU25a	C060	CLU03	C110	CLU20d	C160	CLU26	C210	CLU07	C260	CLU04	C310	CLU06
C010	CLU08	C061	CLU11	C111	CLU20a	C161	CLU43	C211	CLU14	C261	CLU28	C311	CLU16
C011	CLU25a	C062	CLU11	C112	CLU20d	C162	CLU43	C212	CLU14	C262	CLU29	C312	CLU16
C012	CLU08	C063	CLU12	C113	CLU17	C163	CLU43	C213	CLU14	C263	CLU03	C313	CLU16
C013	CLU08	C064	CLU25c	C114	CLU17	C164	CLU43	C214	CLU15	C264	CLU03	C314	CLU16
C014	CLU02	C065	CLU11	C115	CLU38	C165	CLU43	C215	CLU48	C265	CLU34	C315	CLU04
C015	CLU25a	C066	CLU12	C116	CLU38	C166	CLU43	C216	CLU46	C266	CLU29	C316	CLU04
C016	CLU25b	C067	CLU37	C117	CLU39	C167	CLU43	C217	CLU23	C267	CLU34	C317	CLU34
C017	CLU25b	C068	CLU12	C118	CLU27	C168	CLU49	C218	CLU23	C268	CLU05	C318	CLU34
C018	CLU25a	C069	CLU12	C119	CLU27	C169	CLU49	C219	CLU23	C269	CLU40	C319	CLU34
C019	CLU25a	C070	CLU11	C120	CLU09	C170	CLU49	C220	CLU23	C270	CLU21	C320	CLU34
C020	CLU25c	C071	CLU37	C121	CLU24	C171	CLU49	C221	CLU30	C271	CLU19	C321	CLU34
C021	CLU08	C072	CLU11	C122	CLU47	C172	CLU49	C222	CLU30	C272	CLU01	C322	CLU29
C022	CLU12	C073	CLU12	C123	CLU20d	C173	CLU10	C223	CLU30	C273	CLU01	C323	CLU29
C023	CLU08	C074	CLU37	C124	CLU20c	C174	CLU43	C224	CLU30	C274	CLU06	C324	CLU29
C024	CLU25c	C075	CLU35	C125	CLU20a	C175	CLU26	C225	CLU30	C275	CLU06	C325	CLU29
C025	CLU08	C076	CLU37	C126	CLU20a	C176	CLU13	C226	CLU33	C276	CLU16	C326	CLU04
C026	CLU02	C077	CLU37	C127	CLU38	C177	CLU10	C227	CLU33	C277	CLU06	C327	CLU04
C027	CLU25c	C078	CLU11	C128	CLU38	C178	CLU10	C228	CLU33	C278	CLU16	C328	CLU21

C028	CLU25c	C079	CLU12	C129	CLU38	C179	CLU22	C229	CLU33	C279	CLU21	C329	CLU21
C029	CLU25c	C080	CLU12	C130	CLU17	C180	CLU36	C230	CLU33	C280	CLU21	C330	CLU18
C030	CLU35	C081	CLU37	C131	CLU17	C181	CLU36	C231	CLU45	C281	CLU21	C331	CLU18
C031	CLU35	C082	CLU20a	C132	CLU39	C182	CLU42	C232	CLU45	C282	CLU19	C332	CLU41
C032	CLU25c	C083	CLU20c	C133	CLU39	C183	CLU36	C233	CLU45	C283	CLU19	C333	CLU50
C033	CLU25c	C084	CLU20b	C134	CLU47	C184	CLU42	C234	CLU46	C284	CLU21	C334	CLU31
C034	CLU35	C085	CLU20b	C135	CLU24	C185	CLU13	C235	CLU46	C285	CLU05	C335	CLU31
C035	CLU02	C086	CLU39	C136	CLU09	C186	CLU22	C236	CLU46	C286	CLU19	C336	CLU31
C036	CLU02	C087	CLU17	C137	CLU27	C187	CLU13	C237	CLU46	C287	CLU40	C337	CLU31
C037	CLU25c	C088	CLU17	C138	CLU27	C188	CLU49	C238	CLU46	C288	CLU40	C338	CLU31
C038	CLU02	C089	CLU38	C139	CLU27	C189	CLU10	C239	CLU46	C289	CLU40	C339	CLU18
C039	CLU02	C090	CLU38	C140	CLU20b	C190	CLU20c	C240	CLU46	C290	CLU05	C340	CLU18
C040	CLU02	C091	CLU27	C141	CLU20c	C191	CLU20a	C241	CLU07	C291	CLU01	C341	CLU18
C041	CLU08	C092	CLU27	C142	CLU20d	C192	CLU20d	C242	CLU07	C292	CLU01	C342	CLU18
C042	CLU02	C093	CLU24	C143	CLU20c	C193	CLU20c	C243	CLU07	C293	CLU01	C343	CLU18
C043	CLU25a	C094	CLU09	C144	CLU20c	C194	CLU20b	C244	CLU07	C294	CLU01	C344	CLU18
C044	CLU25b	C095	CLU47	C145	CLU49	C195	CLU20d	C245	CLU07	C295	CLU01	C345	CLU18
C045	CLU25c	C096	CLU20b	C146	CLU26	C196	CLU20c	C246	CLU07	C296	CLU01	C346	CLU41
C046	CLU25b	C097	CLU20b	C147	CLU26	C197	CLU22	C247	CLU14	C297	CLU01	C347	CLU41
C047	CLU25a	C098	CLU20b	C148	CLU22	C198	CLU26	C248	CLU14	C298	CLU01	C348	CLU41
C048	CLU02	C099	CLU20a	C149	CLU43	C199	CLU42	C249	CLU14	C299	CLU03	C349	CLU41
C049	CLU02	C100	CLU20a	C150	CLU10	C200	CLU36	C250	CLU14	C300	CLU03	C350	CLU50
C050	CLU08	C101	CLU20a	C151	CLU36	C201	CLU43	C251	CLU14	C301	CLU28	C351	CLU50
												C352	CLU50

Table C.9: Greek case study - Vaccinations centre's data

VC	ζ_{vc}	ι_{vc}^{max}	ι_{vc}^{b}	**VC**	ζ_{vc}	ι_{vc}^{max}	ι_{vc}^{b}	**VC**	ζ_{vc}	ι_{vc}^{max}	ι_{vc}^{b}	**VC**	ζ_{vc}	ι_{vc}^{max}	ι_{vc}^{b}
C001	6300	33	22	C090	6204	32	22	C178	972	5	4	C266	4716	25	17
C002	6300	33	22	C091	6672	35	24	C179	1344	7	5	C267	7956	41	28
C003	6300	33	22	C092	6672	35	24	C180	1044	5	4	C268	7176	37	25
C004	6300	33	22	C093	4776	25	17	C181	1044	5	4	C269	5424	28	19
C005	6300	33	22	C094	3072	16	11	C182	1200	6	5	C270	8328	43	29
C006	6300	33	22	C095	4716	25	17	C183	1044	5	4	C271	4128	22	15
C007	6300	33	22	C096	3168	17	11	C184	1200	6	5	C272	8880	46	31
C008	6300	33	22	C097	3168	17	11	C185	1596	8	6	C273	8880	46	31
C009	6300	33	22	C098	3168	17	11	C186	1344	7	5	C274	10452	54	37
C010	13356	70	47	C099	3168	17	11	C187	816	4	3	C275	10452	54	37
C011	6300	33	22	C100	3168	17	11	C188	924	5	4	C276	7848	41	28
C012	13356	70	47	C101	3168	17	11	C189	1944	10	7	C277	10452	54	37
C013	6696	35	24	C102	3168	17	11	C190	3168	17	11	C278	7848	41	28
C014	7380	38	26	C103	3168	17	11	C191	3168	17	11	C279	8328	43	29
C015	3144	16	11	C104	3168	17	11	C192	3168	17	11	C280	1044	5	4
C016	3144	16	11	C105	3168	17	11	C193	3168	17	11	C281	1044	5	4
C017	6300	33	22	C106	3168	17	11	C194	3168	17	11	C282	516	3	2
C018	6300	33	22	C107	3168	17	11	C195	3168	17	11	C283	516	3	2
C019	6300	33	22	C108	3168	17	11	C196	3168	17	11	C284	1044	5	4
C020	6300	33	22	C109	3168	17	11	C197	2676	14	10	C285	900	5	4
C021	13356	70	47	C110	3168	17	11	C198	1044	5	4	C286	516	3	2
C022	13980	73	49	C111	3168	17	11	C199	2376	12	9	C287	672	4	3
C023	13356	70	47	C112	3168	17	11	C200	2076	11	8	C288	672	4	3
C024	3144	16	11	C113	1620	8	6	C201	2592	14	9	C289	672	4	3

C025	6696	35	24	C114	1620	8	6	C202	1596	8	6	C290	900	5	4
C026	7380	38	26	C115	1548	8	6	C203	1596	8	6	C291	1116	6	4
C027	3144	16	11	C116	1548	8	6	C204	9144	48	32	C292	1116	6	4
C028	3144	16	11	C117	2676	14	10	C205	13080	68	46	C293	1116	6	4
C029	3144	16	11	C118	1668	9	6	C206	13080	68	46	C294	1116	6	4
C030	11556	60	41	C119	1668	9	6	C207	8100	42	29	C295	1116	6	4
C031	11556	60	41	C120	768	4	3	C208	12384	65	43	C296	1116	6	4
C032	3144	16	11	C121	1200	6	5	C209	1692	9	6	C297	1116	6	4
C033	3144	16	11	C122	1188	6	5	C210	6768	35	24	C298	1116	6	4
C034	11556	60	41	C123	1572	8	6	C211	2196	11	8	C299	672	4	3
C035	3696	19	13	C124	792	4	3	C212	8724	45	31	C300	672	4	3
C036	3696	19	13	C125	792	4	3	C213	8724	45	31	C301	1440	8	5
C037	1572	8	6	C126	1572	8	6	C214	1092	6	4	C302	1440	8	5
C038	3696	19	13	C127	792	4	3	C215	1800	9	7	C303	1440	8	5
C039	3696	19	13	C128	792	4	3	C216	4128	22	15	C304	1440	8	5
C040	3696	19	13	C129	792	4	3	C217	2292	12	8	C305	1320	7	5
C041	3348	17	12	C130	816	4	3	C218	1140	6	4	C306	1440	8	5
C042	3696	19	13	C131	816	4	3	C219	1140	6	4	C307	2616	14	10
C043	3144	16	11	C132	1344	7	5	C220	1140	6	4	C308	2616	14	10
C044	3144	16	11	C133	1344	7	5	C221	1644	9	6	C309	996	5	4
C045	3144	16	11	C134	588	3	3	C222	1644	9	6	C310	1320	7	5
C046	3144	16	11	C135	600	3	3	C223	1644	9	6	C311	996	5	4
C047	3144	16	11	C136	396	2	2	C224	1644	9	6	C312	996	5	4
C048	3696	19	13	C137	840	4	3	C225	1644	9	6	C313	996	5	4
C049	3696	19	13	C138	840	4	3	C226	2040	11	8	C314	996	5	4
C050	6696	35	24	C139	840	4	3	C227	2040	11	8	C315	948	5	4
C051	14784	77	52	C140	6300	33	22	C228	2040	11	8	C316	948	5	4

C052	6300	33	22	C141	6300	33	22	C229	8100	42	29	C317	996	5	4
C053	6024	31	21	C142	6300	33	22	C230	2040	11	8	C318	996	5	4
C054	9780	51	34	C143	6300	33	22	C231	1548	8	6	C319	996	5	4
C055	9780	51	34	C144	6300	33	22	C232	1548	8	6	C320	996	5	4
C056	23112	120	81	C145	7344	38	26	C233	1548	8	6	C321	996	5	4
C057	9780	51	34	C146	4176	22	15	C234	2064	11	8	C322	588	3	3
C059	3696	19	13	C147	4176	22	15	C235	2064	11	8	C323	588	3	3
C060	672	4	3	C148	10728	56	38	C236	2064	11	8	C324	588	3	3
C061	1500	8	6	C149	10332	54	36	C237	2064	11	8	C325	588	3	3
C062	3000	16	11	C150	7800	41	28	C238	4128	22	15	C326	948	5	4
C063	6996	36	25	C151	8280	43	29	C239	2064	11	8	C327	948	5	4
C064	1572	8	6	C152	9528	50	34	C240	2064	11	8	C328	1044	5	4
C065	1500	8	6	C153	6396	33	23	C241	864	5	3	C329	1044	5	4
C066	6996	36	25	C154	6396	33	23	C242	864	5	3	C330	13176	69	46
C067	4896	26	17	C155	792	4	3	C243	1692	9	6	C331	13176	69	46
C068	6996	36	25	C156	1572	8	6	C244	1692	9	6	C332	6924	36	25
C069	6996	36	25	C157	792	4	3	C245	864	5	3	C333	14328	75	50
C070	3000	16	11	C158	792	4	3	C246	864	5	3	C334	1944	10	7
C071	4896	26	17	C159	924	5	4	C247	1092	6	4	C335	1944	10	7
C072	1500	8	6	C160	540	3	2	C248	1092	6	4	C336	1944	10	7
C073	6996	36	25	C161	1296	7	5	C249	1092	6	4	C337	1944	10	7
C074	4896	26	17	C162	1296	7	5	C250	2196	11	8	C338	1944	10	7
C075	11556	60	41	C163	1296	7	5	C251	1092	6	4	C339	1644	9	6
C076	4896	26	17	C164	1296	7	5	C252	1092	6	4	C340	1644	9	6
C077	4896	26	17	C165	1296	7	5	C253	1644	9	6	C341	1644	9	6
C078	3000	16	11	C166	1296	7	5	C254	564	3	2	C342	1644	9	6
C079	6996	36	25	C167	1296	7	5	C255	1092	6	4	C343	1644	9	6

C080	6996	36	25	C168	924	5	4	C256	1800	9	7	C344	1644	9	6
C081	4896	26	17	C169	924	5	4	C257	900	5	4	C345	1644	9	6
C082	6300	33	22	C170	924	5	4	C258	900	5	4	C346	888	5	4
C083	6300	33	22	C171	924	5	4	C259	3096	16	11	C347	888	5	4
C084	6300	33	22	C172	924	5	4	C260	7620	40	27	C348	888	5	4
C085	6300	33	22	C173	972	5	4	C261	11496	60	40	C349	888	5	4
C086	10656	56	37	C174	1296	7	5	C262	4716	25	17	C350	1800	9	7
C087	6468	34	23	C175	540	3	2	C263	5304	28	19	C351	1800	9	7
C088	6468	34	23	C176	816	4	3	C264	5304	28	19	C352	1800	9	7
C089	6204	32	22	C177	972	5	4	C265	7956	41	28				

Table C.10: Greek case study - Vaccine's data

Vaccine	**Minimum flow from hub to centres ($\rho_{f,h}^{min}$)**	**Doses per vial (δ_v)**	**Cost ξ_v (RMU)**	**Shelf-life λ_v (days)**
P	975	6	12	5
M	100	10	18	-
A	240	10	1.78	-
J	480	5	8.5	-

Table C.11: Greek case study – Maximum vaccine supply

$\pi_{h,v}^{max}$	**P**	**A**	**J**	**M**
H1	14720	13342	17664	3382
H2	10917	9895	13101	2508
H3	15386	13945	18463	3535
H4	20575	18649	24690	4728
H5	3675	3331	4410	844

Table C.12: Greek Case study - Distance matrix

Hub	**VC**	$\mu_{h,v}$	**Hub**	**VC**	$\mu_{h,v}$	**Hub**	**VC**	$\mu_{h,v}$	**Hub**	**VC**	$\mu_{h,v}$	**Hub**	**VC**	$\mu_{h,v}$
H1	C082	11.757	H1	C168	58.926	H2	C229	66.732	H3	C263	78.607	H4	C032	43.404
H1	C083	12.529	H1	C169	82.174	H2	C230	92.092	H3	C264	70.71	H4	C033	26.644
H1	C084	11.52	H1	C170	69.933	H2	C231	38.039	H3	C265	135.561	H4	C034	10.919
H1	C085	11.498	H1	C171	54.407	H2	C232	33.64	H3	C266	163.674	H4	C035	30.194
H1	C086	43.022	H1	C172	131	H2	C233	16.876	H3	C267	144.603	H4	C036	10.164
H1	C087	40.489	H1	C173	104.362	H2	C253	28.302	H3	C274	118.489	H4	C037	22.019
H1	C088	53.186	H1	C174	74.097	H2	C254	99.752	H3	C275	99.569	H4	C038	22.304
H1	C089	43.799	H1	C175	31.059	H2	C255	73.035	H3	C276	182.963	H4	C039	11.518
H1	C090	22.858	H1	C176	290.544	H2	C259	192.197	H3	C277	109.35	H4	C040	13.177
H1	C096	11.789	H1	C177	128.625	H2	C268	140.429	H3	C278	164.253	H4	C041	24.406
H1	C097	11.582	H1	C178	119.61	H2	C269	158.33	H3	C299	95.636	H4	C042	22.171
H1	C098	10.778	H1	C179	125.057	H2	C270	100.538	H3	C300	74.898	H4	C043	14.016
H1	C099	10.505	H1	C180	149.501	H2	C271	144.637	H3	C301	64.139	H4	C044	16.496
H1	C100	8.582	H1	C181	139.931	H2	C272	121.83	H3	C302	42.558	H4	C045	17.61
H1	C101	9.247	H1	C182	147.348	H2	C273	141.094	H3	C303	58.894	H4	C046	16.584
H1	C102	9.359	H1	C183	135.962	H2	C279	102.421	H3	C304	67.411	H4	C047	12.27
H1	C103	2.52	H1	C184	164.634	H2	C280	75.83	H3	C305	116.321	H4	C048	13.665
H1	C104	10.951	H1	C185	256.601	H2	C281	137.973	H3	C306	101.541	H4	C049	6.452
H1	C105	11.257	H1	C186	100.026	H2	C282	141.81	H3	C307	122.963	H4	C050	11.508
H1	C106	11.433	H1	C187	229.466	H2	C283	126.31	H3	C308	139.923	H4	C051	28.069
H1	C107	14.521	H1	C188	41.086	H2	C284	123.678	H3	C309	168.057	H4	C052	9.424
H1	C108	12.849	H1	C189	96.802	H2	C285	81.57	H3	C310	84.936	H4	C053	6.665
H1	C109	17.702	H1	C190	13.319	H2	C286	154.627	H3	C311	174.536	H4	C054	16.682
H1	C110	15.923	H1	C191	10.744	H2	C287	145.731	H3	C312	147.238	H4	C055	20.452

H1	C111	10	H1	C192	21.684	H2	C288	141.055	H3	C313	154.256	H4	C056	21.093
H1	C112	22.184	H1	C193	13.405	H2	C289	132.368	H3	C314	137.135	H4	C057	20.778
H1	C113	40.714	H1	C194	10.744	H2	C290	89.497	H3	C315	109.615	H4	C059	31.531
H1	C114	52.857	H1	C195	21.606	H2	C291	124.039	H3	C316	118.065	H4	C061	5.099
H1	C115	44.762	H1	C196	12.902	H2	C292	171.395	H3	C317	153.285	H4	C062	17.318
H1	C116	23.684	H1	C197	100.385	H2	C293	193.263	H3	C318	161.924	H4	C063	117.671
H1	C117	39.194	H1	C198	27.859	H2	C294	163.836	H3	C319	137.676	H4	C064	40
H1	C123	18.702	H1	C199	158.81	H2	C295	114.04	H3	C320	162.44	H4	C065	17.318
H1	C124	15.718	H1	C200	133.868	H2	C296	127.197	H3	C321	168.134	H4	C066	7.817
H1	C125	6.337	H1	C201	58.057	H2	C297	148.247	H3	C322	151.227	H4	C067	12.222
H1	C126	5.799	H1	C202	246.553	H2	C298	173.201	H3	C323	161.697	H4	C068	10.781
H1	C127	52.505	H1	C203	192.949	H2	C328	123.601	H3	C324	150.556	H4	C069	14.968
H1	C128	38.539	H2	C091	105.918	H2	C329	143.683	H3	C325	194.231	H4	C070	2.716
H1	C129	58.726	H2	C092	124.499	H3	C060	92.015	H3	C326	119.993	H4	C071	11.874
H1	C130	38.224	H2	C093	120.708	H3	C209	88.192	H3	C327	105.936	H4	C072	5.054
H1	C131	30	H2	C094	79.234	H3	C210	54.637	H4	C001	17.305	H4	C073	13.2
H1	C132	72.7	H2	C095	154.152	H3	C211	50.903	H4	C002	16.656	H4	C074	283.231
H1	C133	21.88	H2	C118	105.482	H3	C212	99.887	H4	C003	16.635	H4	C075	18.283
H1	C140	12.177	H2	C119	121.922	H3	C213	125.45	H4	C004	16.673	H4	C076	11.718
H1	C141	12.642	H2	C120	79.234	H3	C215	99.029	H4	C005	15.737	H4	C077	271.898
H1	C142	21.726	H2	C121	119.073	H3	C216	51.911	H4	C006	17.162	H4	C078	11.757
H1	C143	13.153	H2	C122	154.145	H3	C234	78.388	H4	C007	16.811	H4	C079	12.279
H1	C144	12.252	H2	C134	134.853	H3	C235	84.981	H4	C008	15.809	H4	C080	15.517
H1	C145	53.8	H2	C135	123.678	H3	C236	93.876	H4	C009	13.433	H4	C081	9.243
H1	C146	35.472	H2	C136	69.287	H3	C237	30.286	H4	C010	14.282	H5	C330	7.635
H1	C147	28.701	H2	C137	120	H3	C238	54.271	H4	C011	15.406	H5	C331	3.657
H1	C148	98.649	H2	C138	94.317	H3	C239	46.242	H4	C012	12.867	H5	C332	52.818

H1	C149	61.83	H2	C139	109.251	H3	C240	63.94	H4	C013	15.856	H5	C333	87.257
H1	C150	96.661	H2	C204	9.02	H3	C241	49.118	H4	C014	16.695	H5	C334	38.022
H1	C151	133.526	H2	C205	28.878	H3	C242	101.28	H4	C015	15.774	H5	C335	56.571
H1	C152	159.653	H2	C206	31.206	H3	C243	36.606	H4	C016	15.838	H5	C336	79.237
H1	C153	192.949	H2	C207	65.714	H3	C244	88.27	H4	C017	16.763	H5	C337	30.568
H1	C154	246.553	H2	C208	22.473	H3	C245	40.918	H4	C018	12.893	H5	C338	30.568
H1	C155	34.417	H2	C214	73.977	H3	C246	36.873	H4	C019	13.724	H5	C339	20.323
H1	C156	25.973	H2	C217	7.814	H3	C247	75.906	H4	C020	21.841	H5	C340	17.078
H1	C157	53.945	H2	C218	26.267	H3	C248	95.451	H4	C021	22.215	H5	C341	25.304
H1	C158	37.267	H2	C219	6.783	H3	C249	83.326	H4	C022	13.973	H5	C342	32.171
H1	C159	36.382	H2	C220	7.607	H3	C250	49.592	H4	C023	27.637	H5	C343	22.621
H1	C160	40.474	H2	C221	53.877	H3	C251	57.647	H4	C024	22.727	H5	C344	31.379
H1	C161	96.345	H2	C222	54.934	H3	C252	103.202	H4	C025	21.165	H5	C345	32.8
H1	C162	88.762	H2	C223	51.061	H3	C256	98.722	H4	C026	23.388	H5	C346	24.107
H1	C163	60.957	H2	C224	37.818	H3	C257	105.676	H4	C027	21.247	H5	C347	56.545
H1	C164	81.302	H2	C225	27.704	H3	C258	108.601	H4	C028	38.874	H5	C348	66.464
H1	C165	64.017	H2	C226	55.882	H3	C260	91.349	H4	C029	23.198	H5	C349	41.77
H1	C166	80.952	H2	C227	66.773	H3	C261	42.294	H4	C030	16.409	H5	C350	70.936
H1	C167	46.801	H2	C228	63.53	H3	C262	123.72	H4	C031	24.314	H5	C351	108.823
												H5	C352	120