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SUPPLY CHAIN OPTIMIZATION OF CAR-T CELL THERAPIES

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ΠΕΡΙΛΗΨΗ

Η παρούσα διπλωματική πραγματεύεται την βελτιστοποίηση της εφοδιαστικής αλυσίδας προσωποποιημένων θεραπειών κατά του καρκίνου με χρήση CAR-T κυττάρων. Οι προσωποποιημένες κυτταρικές θεραπείες φαίνονται πολλά υποσχόμενες για την καταπολέμηση πολύ σοβαρών ασθενειών, όπως ο καρκίνος. Πιο συγκεκριμένα οι θεραπείες με CAR-T κύτταρα έχουν δείξει πολύ ενθαρρυντικά αποτελέσματα όσο αφορά τους καρκίνους του αίματος και μάλιστα υπάρχουν ήδη εγκεκριμένες από τον FDA θεραπείες που χρησιμοποιούνται σε περιορισμένο αριθμό ασθενών. Μέσα στα επόμενα χρόνια, η ζήτηση για τέτοιου είδους θεραπείες αναμένεται πως θα αυξηθεί εκθετικά και οι εταιρείες παραγωγής τους , εκτός από τις προκλήσεις παραγωγής της θεραπείας αυτής καθ' αυτής θα έχουν να αντιμετωπίσουν και προβλήματα σχετικά με την αύξηση της παραγωγικής δραστηριότητας. Όλα τα παραπάνω υπογραμμίζουν την ανάγκη για τη χρήση προηγμένων υπολογιστικών εργαλείων που θα βοηθήσουν τις σχετικές εταιρείες στη λήψη αποφάσεων και στον καλύτερο σχεδιασμό της παραγωγής αλλά και της διανομής των προϊόντων τους. Οι μηχανικοί παραδοσιακά έχουν συμβάλλει τη φαρμακοβιομηχανία σε θέματα που αφορούν τα συστήματα διεργασιών και το σχεδιασμό τους και θα ανταποκριθούν και στην παρούσα πρόκληση των νέων βιοφαρμακευτικών προϊόντων. Οι κυτταρικές θεραπείες με CAR T κύτταρα είναι ακόμα πολύ ακριβές για να παραχθούν μαζικά για τρεις κυρίως λόγους: (1) είναι αυτόλογες θεραπείες και η πρώτη ύλη είναι διαφορετική για κάθε θεραπεία, (2) έχουν υψηλά κόστη διανομής, καθώς απαιτούν ειδική μεταχείρισή κατά τη μεταφορά τους και τα διαθέσιμα εργαστήρια παραγωγής δεν είναι πάντα κοντά στα νοσοκομεία (3) η χωρητικότητα των υπάρχοντών μονάδων παραγωγής είναι πολύ περιορισμένη. Συνεπώς, η δημιουργία και χρήση ενός MILP μοντέλου ικανού να προτείνει ένα βέλτιστο δίκτυο εφοδιαστικής αλυσίδας θα επιτρέψει την κλιμάκωση της παραγωγής και τη μείωση του κόστους των θεραπειών. Ένα ακόμα πρόβλημα σχετικά με τις θεραπείες αυτές και τον σχεδιασμό της εφοδιαστικής τους αλυσίδας είναι ότι η ζήτηση δεν είναι προβλέψιμη, καθώς η αγορά είναι πολύ καινούρια και τώρα αναπτύσσεται. Συνεπώς, τα προτεινόμενα δίκτυα θα πρέπει να είναι εύρωστα και να μπορούν να διαχειριστούν διακυμάνσεις στη ζήτηση. Στη συνέχεια παρουσιάζονται με τη σειρά οι ερευνητικοί στόχοι, σχεδιάζονται τα κατάλληλα MILP μοντέλα για τον καθένα και παρουσιάζονται τα αντίστοιχα αποτελέσματα. Οι τρεις κύριοι άξονες στους οποίους εστιάζει η παρούσα εργασία είναι: πολύ-παραγοντική βελτιστοποίηση για καθορισμό του βέλτιστου δικτύου, μεγιστοποίηση του αριθμού ασθενών που μπορεί να εξυπηρετήσει το κάθε δίκτυο αν επιτρέπεται η βέλτιστη κατανομή των ασθενών στα κέντρα λευκαφαίρεσης και εισαγωγή της δυνατότητας αναμονής σε περίπτωση

κορεσμού του δικτύου, γεγονός που κάνει το μοντέλο πιο ρεαλιστικό σε σύγκριση με τα προηγούμενα όπου ήταν ιδεατά, χωρίς καθόλου καθυστερήσεις. Τα παραπάνω πραγματοποιούνται για τρία διαφορετικά ύψη ζήτησης και μεγέθους δικτύων και αφορούν τις CAR T κυτταρικές θεραπείες και τη διανομή τους στην Αγγλία.

ABSTRACT

Personalized Cell Therapies form a novel class of biologic therapeutics which pave the way to treatment of life-threatening diseases, such as cancer. CAR-T cells are currently at the forefront of cell therapies targeting blood cancers and there already are FDA approved therapies being used in a small number of patients; the demand for CAR-T cell therapies is continuously increasing and manufacturers must tackle difficulties concerning the engineering of product and the production process, while scaling up their production. This highlights the need for sophisticated decision-making tools, which enable effective manufacturing and distribution planning throughout product lifetimes. Process systems engineering (PSE) has traditionally assisted the pharmaceutical industry in the development of such tools. CAR-T cell therapies at present are very expensive due to the following reasons: (1) they are autologous therapies and raw materials are different for each therapy, (2) they have increased logistic costs due to the need of special handling during transportation and because manufacturing sites are not always close to hospitals (3) capacity of existing manufacturing facilities is limited. As a result, the optimization of their supply chain using a MILP model can indicate optimal network structures that can be established and will enable up-scaling of their production while reducing manufacturing and logistics costs. Computational challenges also emerge due to the demand uncertainty that characterizes this new industry that is still developing. Subsequently, the development of robust supply chain networks able to absorb shocks in the demand is imperative. A series of research objectives is proposed, followed by the design of different MILP models for each of them and the presentation of relevant results. The three focus areas of this thesis are: multi-objective optimization for an optimal network determination, demand maximization and supply chain robustness when network is fixed and optimal allocation of patients in the leukapheresis site is allowed and introduction of waiting time to an otherwise ideal supply chain without delays. The design focuses on the UK CAR-T cell therapies supply chain and evaluates three different demand levels and network sizes. This thesis is conducted in the Industrial Process Systems Engineering Unit (IPSEN) of NTUA directed by Professor Kokossis and in collaboration with Professor Papathanasiou from Centre for Process Systems Engineering (CPSE) of Imperial College London. The project is conducted under the umbrella of the UK Engineering & Physical Sciences Research Council (EPSRC) for the Future Targeted Healthcare Manufacturing Hub.

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ΣΥΝΟΨΗ

Ως εφοδιαστική αλυσίδα ορίζεται ένα δίκτυο εγκαταστάσεων που εκτελεί τις λειτουργίες προμήθειας υλικών, μετατροπής αυτών των υλικών σε ενδιάμεσα και τελικά προϊόντα και διανομής αυτών των προϊόντων στους πελάτες[7]. Η οργάνωση της εφοδιαστικής αλυσίδας είναι μια από τις βασικές λειτουργίες μιας επιχείρησης, επειδή διασφαλίζει ότι τα προϊόντα θα φτάσουν στους τελικούς πελάτες και συνεπώς θα επιτευχθεί κερδοφορία. Μια τυπική αλυσίδα εφοδιασμού περιλαμβάνει προμηθευτές, εγκαταστάσεις παραγωγής, εγκαταστάσεις αποθήκευσης και πελάτες. Ωστόσο, η διαχείριση τέτοιων συστημάτων είναι αρκετά περίπλοκη λόγω της πολλαπλότητας των ροών υλικών και πληροφοριών, των διαφοροποιημένων χαρακτηριστικών των οντοτήτων και των συχνά παρόντων αντικρουόμενων στόχων.[1]

Οι κύριοι στόχοι του σχεδιασμού μιας αποτελεσματικής αλυσίδας εφοδιασμού περιλαμβάνουν: (i) ελαχιστοποίηση του κόστους, των καθυστερήσεων παράδοσης και των αποθεμάτων, (ii) μεγιστοποίηση του κέρδους, της απόδοσης επένδυσης (ROI), του επιπέδου εξυπηρέτησης πελατών και της παραγωγής. Για να επιτευχθούν αυτοί οι στόχοι, πρέπει να ληφθούν αποφάσεις τοποθεσίας, παραγωγής, απογραφής και μεταφοράς. [2]

Τα προβλήματα που αφορούν την εφοδιαστική αλυσίδα μπορούν να χωριστούν σε τρεις κατηγορίες: (i) Σχεδιασμός υποδομής εφοδιαστικής αλυσίδας (δίκτυο). (ii) ανάλυση της εφοδιαστικής αλυσίδας και διαμόρφωση πολιτικής. (iii) προγραμματισμός της εφοδιαστικής αλυσίδας, ώστε να ανταποκρίνεται καλύτερα σε εξωγενείς παράγοντες επίδρασης. [4]

Η διαχείριση της εφοδιαστικής αλυσίδας είναι πολύ απαιτητική και η ανάγκη για υπολογιστικά εργαλεία ικανά να βοηθήσουν στη λήψη αποφάσεων φαίνεται επιτακτική.

Οι απαιτήσεις της αγοράς και της κοινωνίας συνεχίζουν να αυξάνονται και ως εκ τούτου οι σύγχρονες αλυσίδες εφοδιασμού πρέπει να αντιμετωπίσουν νέες προκλήσεις (μικρότερους κύκλους ζωής προϊόντων, μαζική προσαρμογή, εξατομικευμένα προϊόντα και ανάγκη για πιο βιώσιμες διαδικασίες και προϊόντα). [1,4]

Συνεπώς απαιτείται η ανάπτυξη υπολογιστικών εργαλείων που εξασφαλίζουν την απαιτούμενη ευελιξία της εφοδιαστικής αλυσίδας.

Τα είδη μοντελοποίησης μεταξύ άλλων περιλαμβάνουν:

(1)Ευρετικούς αλγορίθμους (Heuristic-based approaches), (2) γραμμικό προγραμματισμό (LP, αντιμετωπίζονται προβλήματα με γραμμική αντικειμενική συνάρτηση και γραμμικά διατυπωμένους περιορισμούς. Στον γραμμικό προγραμματισμό δεν υπάρχει χαρακτηριστικός αναλυτικός τύπος αλλά υπάρχει μια ποικιλία μεθόδων όπως η μέθοδος Simplex και οι μέθοδοι εσωτερικού σημείου), (3) προγραμματισμό μικτών ακεραίων (MILP, μελετά γραμμικά προγράμματα στα οποία ορισμένες μεταβλητές περιορίζονται να λαμβάνουν μόνο ακέραιες τιμές. Σε πολλές περιπτώσεις MILP οι ακέραιες μεταβλητές είναι δυαδικές (0-1 μεταβλητές). Για κάθε συνδυασμό δυαδικών, προκύπτει ένα διαφορετικό πρόβλημα βελτιστοποίησης. Οι πιο συνηθισμένοι αλγόριθμοι για την αντιμετώπιση MILP προβλημάτων είναι: η μέθοδος διακλάδωσης και δέσμευσης, η μέθοδος του επιπέδου κοπής, διάφοροι μέθοδοι αποσύνθεσης και μέθοδοι βασισμένες στη λογική), (4) μη γραμμικό προγραμματισμό (μελετάται η γενική περίπτωση κατά την οποία η αντικειμενική συνάρτηση ή οι περιορισμοί ή και τα δύο αποτελούνται από μη γραμμικά στοιχεία), (5) τετραγωνικό προγραμματισμό (QP) (εξετάζει προβλήματα των οποίων η αντικειμενική συνάρτηση έχει τετραγωνικούς όρους, ενώ το εφικτό σύνολο καθορίζεται με γραμμικές ισότητες και ανισότητες), (6) δυναμικό προγραμματισμό (ένα σύνθετο πρόβλημα μετατρέπεται σε μια ακολουθία απλούστερων προβλημάτων), (7) στοχαστικό προγραμματισμό (τέτοια προβλήματα έχουν περιορισμούς ή παραμέτρους ανάλογα με τυχαίες μεταβλητές).

Παρατηρείται ότι τα περισσότερα προβλήματα που αφορούν εφοδιαστικές αλυσίδες διατυπώνονται ως μοντέλα MILP, αφού η περιγραφή τους βασίζεται σε μεγάλο βαθμό σε απλά μοντέλα εισροών-εκροών. Επιπλέον, ενώ αρχικά τα μοντέλα διατυπώνονται ως ντετερμινιστικά, συχνά υπάρχει η ανάγκη να λαμβάνονται υπόψη οι αβεβαιότητες, που εκτείνονται από την αβεβαιότητα της ζήτησης και τη διαθεσιμότητα του εξοπλισμού έως τις ρυθμίσεις προγραμματισμού και τις τιμές. [9]

Ένα άλλο σημαντικό στοιχείο που εμπλέκεται στη μαθηματική μοντελοποίηση και προγραμματισμό είναι οι επιλύτες (solvers) που χρησιμοποιούνται. Σε αυτή τη διπλωματική χρησιμοποιείται ο CPLEX της IBM. Ο CPLEX είναι ηγέτης στην επίλυση προβλημάτων γραμμικού προγραμματισμού, όπως ο προγραμματισμός μεικτών ακεραίων.

Η θεραπεία με κύτταρα CAR-T είναι μια νέα και ισχυρή τεχνική που βασίζεται στην ανοσοθεραπεία, με ενθαρρυντικά αποτελέσματα στη θεραπεία του καρκίνου. Τέτοιες θεραπείες χρησιμοποιούν το ανοσοποιητικό σύστημα του ίδιου του ασθενούς για να στοχεύσουν και να καταπολεμήσουν τον καρκίνο. [11]

Τα ανοσοκύτταρα μπορούν να παραχθούν στο εργαστήριο υπό αυστηρά ελεγχόμενες συνθήκες και στη συνέχεια να χορηγηθούν σε ασθενείς για τη θεραπεία του καρκίνου. Αρκετοί τύποι ανοσοθεραπειών είτε έχουν εγκριθεί για χρήση είτε βρίσκονται υπό μελέτη σε κλινικές δοκιμές για να προσδιοριστεί η αποτελεσματικότητά τους στη θεραπεία διαφόρων τύπων καρκίνου. [12]

Τα Τ-κύτταρα, αν και αποτελεσματικά στην καταπολέμηση των λοιμώξεων, δεν μπορούν εύκολα να αναγνωρίσουν τα καρκινικά κύτταρα και έτσι τα τελευταία αποφεύγουν την ανοσολογική απόκριση και συνεχίζουν να αναπτύσσουν τον καρκίνο. Οι επιστήμονες εργάζονται για την εισαγωγή του χιμαιρικού υποδοχέα αντιγόνου στα Τ κύτταρα για να ενισχύσουν τη στόχευσή τους στα καρκινικά κύτταρα. Τα κύτταρα με τον υποδοχέα CAR μπορούν να αναγνωρίζουν και να στοχεύουν μια συγκεκριμένη πρωτεΐνη στα καρκινικά κύτταρα.

Το πρώτο βήμα στη διαδικασία παραγωγής κυτταρικών θεραπειών είναι η λευκαφαίρεση, όπου τα Τ-κύτταρα εξάγονται από το αίμα του ασθενούς. Η ασθένεια, η προχωρημένη ηλικία, η προηγούμενη θεραπεία και τα χαρακτηριστικά του περιφερικού αίματος (λεμφοπενία, υψηλό φορτίο περιφερικής νόσου) μπορεί να οδηγήσουν σε μειωμένη ποιότητα ή ποσότητα κυττάρων CAR-T στο τελικό προϊόν. Ακολουθεί ο εμπλουτισμός των κυττάρων. Αυτό μπορεί να γίνει χρησιμοποιώντας τεχνικές απομάκρυνσης (βαθμίδα πυκνότητας, έκλουση αντίθετης ροής, τεχνικές προσκόλλησης φιάλης) ή τεχνικές επιλογής κυττάρων (συζεύγματα φθοριοχρωμάτων αντισώματος, συζυγή αντισώματος-μαγνητικού σφαιριδίου, μέθοδοι απομόνωσης με βάση το επταμερές). Το τρίτο βήμα είναι η ενεργοποίηση κυττάρων που εξαρτάται από τον τύπο των διεγερτικών αντιδραστηρίων και τη διάρκεια της ενεργοποίησης. Ακολουθεί η μεταφορά του γονιδίου CAR. Αυτό μπορεί να συμβεί χρησιμοποιώντας ιικά συστήματα (γ-ρετροϊικοί φορείς, φακοϊικοί φορείς) ή μη ιικά συστήματα (ηλεκτροδιάτρηση, στοχευμένες στρατηγικές εισαγωγής όπως νουκλεάση δακτύλου ψευδαργύρου, νουκλεάσες τελεστών που μοιάζουν με ενεργοποιητές μεταγραφής, CRISPR-CAS9). Ακολουθεί ο πολλαπλασιασμός των κυτάρων. Κατά τη διάρκεια αυτού του σταδίου το θρεπτικό μέσο συμπληρώνεται με κυτοκίνες για την ενίσχυση του ex-vivo πολλαπλασιασμού των κυττάρων CAR-T. Ο τύπος και οι δόσεις των κυτοκινών μπορεί να επηρεάσουν σοβαρά την ποιότητα

του προϊόντος. Επίσης, η διάρκεια της καλλιέργειας θα πρέπει να παρακολουθείται καθώς περισσότερες ημέρες καλλιέργειας οδηγούν σε μεγαλύτερη διαφοροποίηση και λιγότερη ικανότητα θανάτωσης του καρκινικού όγκου. Η επέκταση μπορεί να εκτελεστεί σε βιοαντιδραστήρες ή πλατφόρμες καλλιέργειας. Συγκεκριμένα, μπορούν να χρησιμοποιηθούν συστήματα φιαλών, σάκοι κλειστού συστήματος, μερικώς και πλήρως αυτοματοποιημένα συστήματα (CliniMACs prodigy, Cocoon). Το τελευταίο βήμα περιλαμβάνει την κρυοσυντήρηση και την απόψυξη του τελικού προϊόντος, όπου πρέπει να καθοριστεί ο τύπος και η συγκέντρωση του κρυοπροστατευτικού, η μέθοδος κατάψυξης, οι συνθήκες αποθήκευσης και η μέθοδος, η διάρκεια και ο ρυθμός απόψυξης.

Ο Οργανισμός Τροφίμων και Φαρμάκων των ΗΠΑ (FDA) το 2017 και ο Ευρωπαϊκός Οργανισμός Φαρμάκων (EMA) το 2018 ενέκριναν το KYMRIAHTM της Novartis, την πρώτη αυτόλογη θεραπεία με CAR T κύτταρα. Στη συνέχεια, το YESCARTATM της Kite Pharma ήταν η δεύτερη θεραπεία με CAR T κύτταρα που εγκρίθηκε από τον FDA και τον EMA το 2017 και το 2018 αντίστοιχα. Τέλος, το TECARTUSTM, μια άλλη ανοσοθεραπεία με βάση τα κύτταρα από την Kite Pharma, και η BREYANZITM από τη Bristol Myers Squibb πήραν έγκριση από τον FDA τον Ιούλιο του 2020 και τον Φεβρουάριο του 2021 αντίστοιχα.[15]

Η τιμή καταλόγου των ΗΠΑ για τις εγκεκριμένες θεραπείες κυμαίνεται μεταξύ $373.000 και $475.000. Οι υψηλές τιμές αυτών των θεραπειών αντικατοπτρίζουν το όφελος που προσφέρουν καθώς και το κόστος που σχετίζεται με την κατασκευή, τη διανομή και τη χορήγηση του προϊόντος.

Τα κύρια βήματα ενός τυπικού κύκλου ζωής θεραπείας με κύτταρα CAR T είναι: (α) αναγνώριση του ασθενούς, (β) λευκαφαίρεση, (γ) παραγωγή, (δ) ποιοτικός έλεγχος, (ε) χορήγηση θεραπείας.

Η αναγνώριση του ασθενούς περιλαμβάνει την παρακολούθηση και τον έλεγχο του προϊόντος κάθε ασθενούς από τη λευκαφαίρεση έως την έγχυση, διασφαλίζοντας την ασφαλή παράδοση της σωστής θεραπείας στον κατάλληλο ασθενή.[16] Το πρώτο βήμα είναι η συλλογή μονοπύρηνων κυττάρων περιφερικού αίματος (PBMC) από τον ασθενή (αυτόλογα) ή δότη (αλλογενή) με λευκαφαίρεση, μια μέθοδος που διαχωρίζει τα λευκοκύτταρα από το αίμα.[4] Η διαδικασία αυτή γίνεται σε εξειδικευμένα κλινικά κέντρα. Στη συνέχεια, εντός 24 ωρών μετά τη συλλογή, το υλικό λευκαφαίρεσης υποβάλλεται σε διαδικασία κατάψυξης και αποστέλλεται, είτε φρέσκο στους -80 ^{o}C είτε κρυοσυντηρημένο στους -120 ^{o}C, στον τόπο παραγωγής, όπου μπορεί να αποθηκευτεί πριν υποβληθεί σε περαιτέρω επεξεργασία.[25,35] Η διαδικασία κατασκευής ακολουθεί όπως περιγράφεται παραπάνω. Μετά την ολοκλήρωση

της παραγωγικής διαδικασίας πραγματοποιείται ο ποιοτικός έλεγχος. Το τελικό προϊόν υποβάλλεται σε δοκιμές κρίσιμων ποιοτικών χαρακτηριστικών (CQAs), οι οποίες μπορούν να διεξαχθούν είτε στο εργαστήριο παραγωγής είτε σε διαφορετική εγκατάσταση. Τέλος, η κρυοσυντηρημένη θεραπεία με CAR T κύτταρα μεταφέρεται στην κλινική. Πριν από τη χορήγηση της θεραπείας, ο ασθενής πρέπει να υποβληθεί σε χημειοθεραπεία. Μόλις ολοκληρωθεί η προετοιμασία, που μπορεί να διαρκέσει έως και 1 εβδομάδα, τα κύτταρα αποψύχονται και εγχέονται αμέσως στον ασθενή. [16] Μετά τη χορήγηση, οι ασθενείς παρακολουθούνται στενά για παρενέργειες που σχετίζονται με τη θεραπεία, όπως σύνδρομο απελευθέρωσης κυτοκίνης και νευροτοξικότητα. [14]

Εκτός από την ελαχιστοποίηση του κόστους, ο χρόνος παράδοσης των θεραπειών είναι ένας πιεστικός παράγοντας που πρέπει να λαμβάνεται υπόψη κατά το σχεδιασμό της εφοδιαστικής αλυσίδας. Στις εμπορικές θεραπείες, ο χρόνος παράδοσης κυμαίνεται μεταξύ 15-24 ημερών. [28]

Από τα παραπάνω είναι προφανές ότι ψηφιακά εργαλεία όπως η μαθηματική μοντελοποίηση μπορούν να βοηθήσουν στη λήψη αποφάσεων και στον εντοπισμό βέλτιστων δομών δικτύου που θα εξασφαλίσουν ελαχιστοποίηση του κόστους και του χρόνου παράδοσης των θεραπειών.

Η βελτιστοποίηση στοχεύει στην εύρεση της βέλτιστης λύσης που ελαχιστοποιεί την αντικειμενική συνάρτηση αλλάζοντας τις μεταβλητές σχεδιασμού και ικανοποιώντας ταυτόχρονα ορισμένους περιορισμούς. Κατά τη βελτιστοποίηση σχεδιασμού πρέπει να λαμβάνονται υπόψη ταυτόχρονα πολλά κριτήρια σχεδιασμού και πολλαπλές αντικειμενικές συναρτήσεις. Για παράδειγμα, στην περίπτωση των θεραπειών με CAR-T κύτταρα, το κόστος και ο χρόνος επιστροφής πρέπει να ελαχιστοποιηθούν. Όταν βελτιστοποιούνται περισσότεροι από ένας στόχοι, η βελτιστοποίηση γίνεται πολλαπλών στόχων, οπότε δεν μπορεί να χρησιμοποιηθεί η συνήθης βελτιστοποίηση σχεδίασης. (Kim and de Weck)

Η πολυκριτηριακή βελτιστοποίηση είναι αναπόσπαστο μέρος των προβλημάτων βελτιστοποίησης και έχει τεράστιες εφαρμογές, καθώς σχεδόν όλα τα προβλήματα βελτιστοποίησης της πραγματικής ζωής περιγράφονται από πολλούς αντικρουόμενους στόχους.

Το γενικό πρόβλημα βελτιστοποίησης πολλαπλών στόχων τίθεται ως εξής:

$$\text{Min/max } f_m(x) \text{ , } m=1,2,3\ldots m$$

$$\text{Subject to } g_j(x) \geq 0,\ j=1,2,3\ldots j$$

$$h_k(x) = 0,\ k=1,2,3\ldots k$$

όπου m είναι ο αριθμός των αντικειμενικών συναρτήσεων, j είναι ο αριθμός των περιορισμών ανισότητας και k είναι ο αριθμός των περιορισμών ισότητας.

Σε αντίθεση με τη βελτιστοποίηση ενός στόχου, στη βελτιστοποίηση πολλαπλών στόχων συνήθως, δεν υπάρχει ενιαία συνολική λύση και είναι συχνά απαραίτητο να καθοριστεί ένα σύνολο σημείων που ταιριάζουν σε έναν προκαθορισμένο ορισμό για ένα βέλτιστο. Η κυρίαρχη έννοια στον ορισμό ενός βέλτιστου σημείου είναι αυτή του Pareto βέλτιστου, η οποία ορίζεται ως εξής: Pareto Optimal είναι ένα σημείο, $x* \in X$, εάν δεν υπάρχει άλλο σημείο, $x \in X$, έτσι ώστε $F(x) \leq F(x*)$, και $Fi(x) < Fi(x*)$ για τουλάχιστον μία συνάρτηση. [19]

Με πιο απλά λόγια, στο πρόβλημα βελτιστοποίησης ενός στόχου, η υπεροχή μιας λύσης έναντι άλλων λύσεων προσδιορίζεται εύκολα συγκρίνοντας τις τιμές της αντικειμενικής συνάρτησης. Στο πρόβλημα βελτιστοποίησης πολλαπλών στόχων, η καταλληλότητα μιας λύσης καθορίζεται από την κυριαρχία. Για παράδειγμα, το x1 κυριαρχεί στο x2, εάν η Λύση x1 δεν είναι χειρότερη από τη x2 σε όλους τους στόχους ή η Λύση x1 είναι αυστηρά καλύτερη από τη x2 σε τουλάχιστον έναν στόχο. [20]

Δεδομένου ενός συνόλου λύσεων, το σύνολο μη κυριαρχούμενων λύσεων είναι το σύνολο όλων των λύσεων που δεν κυριαρχούνται από κανένα μέλος του συνόλου λύσεων. Το μη κυριαρχούμενο σύνολο ολόκληρου του εφικτού χώρου απόφασης ονομάζεται βέλτιστο σύνολο Pareto. Το όριο που ορίζεται από το σύνολο όλων των σημείων που απεικονίζονται από το βέλτιστο σύνολο Pareto ονομάζεται βέλτιστο σύνορο Pareto.

Το μοντέλο που εξετάζεται σε αυτή την εργασία είναι ένα μοντέλο γραμμικού προγραμματισμού μεικτών ακεραίων (MILP) που περιγράφει την εφοδιαστική αλυσίδα των κυττάρων CAR T και χρησιμοποιείται για τον προσδιορισμό της βέλτιστης δομής δικτύου εφοδιαστικής αλυσίδας για την ασφαλή και έγκαιρη παράδοση των θεραπειών. Το αρχικό μοντέλο αναπτύχθηκε από το εργαστήριο της καθηγήτριας Παπαθανασίου στο Imperial College London.[18] Το δίκτυο της εφοδιαστικής αλυσίδας περιλαμβάνει 4 κόμβους: κέντρο λευκαφαίρεσης, εργοστάσιο παραγωγής, ποιοτικό έλεγχο και νοσοκομείο.

Πιο συγκεκριμένα, ένας ασθενής τοποθετείται σε εξειδικευμένο κέντρο λευκαφαίρεσης, όπου τα Τ κύτταρα απομονώνονται από την κυκλοφορία του αίματος. Στη συνέχεια, τα κύτταρα κρυοσυντηρούνται και μεταφέρονται στην εγκατάσταση παραγωγής. Μετά την επεξεργασία και την επέκταση των κυττάρων, η τελική θεραπεία υποβάλλεται σε έλεγχο ποιότητας. Στο μοντέλο που εστιάζει η παρούσα διπλωματική, ο ποιοτικός έλεγχος

συστεγάζεται με την εγκατάσταση παραγωγής. Εάν τα κύτταρα CAR-T περάσουν επιτυχώς τον έλεγχο, κρυοσυντηρούνται και μεταφέρονται πίσω στο νοσοκομείο όπου θα χορηγηθούν ξανά στον ασθενή. Ακόμη, το νοσοκομείο συστεγάζεται με το σημείο της λευκαφαίρεσης. Ο στόχος του μοντέλου είναι να ελαχιστοποιήσει το συνολικό κόστος των θεραπειών υπό ορισμένους δεδομένους περιορισμούς.

Στο αρχικό μοντέλο, η απόδοση του δικτύου αξιολογείται για διαφορετικά σενάρια ζήτησης (20, 50, 125 ασθενείς ανά 130 ημέρες) και διαφορετικούς χρόνους παράδοσης (17, 18 και 19 ημέρες). Σε αυτό το σημείο, τα προφίλ ζήτησης δημιουργούνται τυχαία από έναν εσωτερικό αλγόριθμο και οι συντελεστές κόστους είναι σταθεροί. Η μελέτη λαμβάνει υπόψη 4 τοποθεσίες λευκαφαίρεσης και 4 νοσοκομεία στο Ηνωμένο Βασίλειο και 6 εγκαταστάσεις παραγωγής στο Ηνωμένο Βασίλειο, την Ευρώπη και την Αμερική. Ο χρόνος κατασκευής έχει οριστεί να είναι 7 ημέρες.

Οι είσοδοι για το μοντέλο περιλαμβάνουν, ένα σύνολο ασθενών, ένα σύνολο θέσεων λευκαφαίρεσης, ένα σύνολο πιθανών τοποθεσιών παραγωγής, ένα σύνολο τρόπων μεταφοράς και ένα σύνολο χρονικών περιόδων.

Αντίστοιχα Το μοντέλο καθορίζει:

• τον αριθμό και την τοποθεσία των εγκαταστάσεων παραγωγής που θα δημιουργηθούν.

• την ανάθεση και σειρά θεραπειών στις εγκαταστάσεις παραγωγής σε κάθε χρονική περίοδο.

• τον προγραμματισμό στα εργαστήρια.

• τους τρόπους μεταφοράς για τη σύνδεση των χώρων παραγωγής με τους χώρους λευκαφαίρεσης και τα νοσοκομεία αντίστοιχα.

Το πρώτο μέρος της παρούσας διπλωματικής εστιάζει στην πολυκριτηριακή βελτιστοποίηση της εφοδιαστικής αλυσίδας των θεραπειών με CAR-T κύτταρα. Στο μοντέλο που περιγράφεται παραπάνω υπάρχουν δύο αντικρουόμενοι στόχοι, η ελαχιστοποίηση του κόστους και η ελαχιστοποίηση του χρόνου επιστροφής των θεραπειών. Συνεπώς, είναι σημαντικό να αξιολογηθεί η αντιστάθμιση μεταξύ των δύο στόχων. Από τη μία πλευρά, η ελαχιστοποίηση του κόστους είναι πολύ σημαντική, αφού οι θεραπείες με κύτταρα CAR-T είναι πολύ ακριβές. Από την άλλη πλευρά, ο χρόνος επιστροφής πρέπει επίσης να ελαχιστοποιηθεί, γιατί αυτές οι θεραπείες απευθύνονται σε ασθενείς με καρκίνο στο τελικό στάδιο που όσο πιο γρήγορα λάβουν τη θεραπεία τους τόσο το καλύτερο. Ο στόχος του νέου μοντέλου είναι να εκφράσει τις πιθανές λύσεις ως ένα σύνολο βέλτιστων pareto σημείων. Για να γίνει αυτό, θα αξιολογηθούν δύο μέθοδοι. Η μία είναι η μέθοδος του σταθμισμένου

αθροίσματος, όπου οι δύο στόχοι εκφράζονται σε μια ενιαία αντικειμενική συνάρτηση και καθένας από αυτούς πολλαπλασιάζεται με έναν παράγοντα βάρους. Η δεύτερη είναι η μέθοδος epsilon constraint, όπου μόνο ο ένας στόχος εκφράζεται στην αντικειμενική συνάρτηση και ο άλλος περιορίζεται κάτω από την τιμή έψιλον. Τα αποτελέσματα κάθε μεθόδου θα συγκριθούν για να εντοπιστεί η πιο αποτελεσματική.

Ακόμη, σε έναν κλάδο όπως αυτός των CAR T θεραπειών, η ζήτηση μπορεί να είναι απροσδόκητη, επομένως είναι πολύ σημαντικό να ελεγχθεί η ικανότητα καθενός από τα προτεινόμενα δίκτυα να απορροφά μη αναμενόμενη ζήτηση.

Επίσης, σημαντικό είναι να διερευνηθεί η μεγιστοποίηση της αξιοποίησης κάθε μονάδας παραγωγής. Πρώτον, τα τρία δίκτυα που προκύπτουν από το μοντέλο πολυκριτηριακής βελτιστοποίησης θα δοκιμαστούν υπό αβέβαιη ζήτηση για να ελεγχθεί η υψηλότερη ζήτηση στην οποία μπορούν να ανταποκριθούν. Για να γίνει αυτό αναπτύσσεται ένα νέο μοντέλο όπου το δίκτυο είναι δεδομένο και σταθερό αλλά δεν δίνεται το προφίλ ζήτησης. Ο χρήστης εισάγει τη συνολική ζήτηση (π.χ. 50 ασθενείς) και το μοντέλο πρέπει να τους κατανείμει με τον βέλτιστο τρόπο για να εξυπηρετήσει όλους ή τους περισσότερους από αυτούς. Έτσι, ελέγχονται διαφορετικοί όγκοι ζήτησης για κάθε δίκτυο, έως ότου το μοντέλο καταστεί άλυτο.

Όταν βρεθεί η μέγιστη ζήτηση, ελέγχεται ποιος από τους κόμβους θα κορεστεί πρώτος, γεγονός που σημαίνει ότι αυτός ο κόμβος μπλοκάρει ολόκληρο το δίκτυο. Γίνεται η υπόθεση ότι υπήρχε ένα περιθώριο ασφαλείας 25% που είχε επιβληθεί στην τρέχουσα χωρητικότητα, το οποίο θα απελευθερωθεί στις ακόλουθες περιπτώσεις. Τα αποτελέσματα θα αναφέρουν πώς ένα τέτοιο περιθώριο μεταφράζεται στην ικανότητα των δικτύων να αντιμετωπίσουν συνολικά υψηλότερη ζήτηση. Επίσης, θα φανεί ποιες μονάδες πρέπει να είναι γίνουν over-designed για να απορροφούν τους κραδασμούς στη ζήτηση.

Ακόμη, μια συνήθης διαδικασία στη βιομηχανία είναι η ενοικίαση μέρους των εγκαταστάσεων άλλων κατασκευαστών αντί της δημιουργίας νέων. Είναι πολύ χρήσιμο να αξιολογηθεί πώς ένα δίκτυο με συνολικά την ίδια χωρητικότητα χωρισμένη σε διαφορετικές εγκαταστάσεις παραγωγής θα ανταποκριθεί σε διαφορετικά επίπεδα ζήτησης.

Τέλος, σχεδιάζεται ένα πιο ρεαλιστικό μοντέλο με καθυστερήσεις. Ο τελευταίος γύρος πειραμάτων περιλαμβάνει μια πιο ρεαλιστική προσέγγιση, όπου οι ασθενείς μπορεί να αντιμετωπίσουν καθυστερήσεις και χρόνο αναμονής πριν από κάθε διαδικασία. Σε όλα τα παραπάνω σενάρια όταν ένας ασθενής εισέρχεται στο νοσοκομείο για τη λευκαφαίρεση,

εξυπηρετείται αμέσως. Αυτό σημαίνει ότι εάν φτάσει ένας ασθενής και η μονάδα παραγωγής είναι πλήρης, το μοντέλο αναγκάζεται να ιδρύσει μία νέα. Αυτό οδηγεί σε αύξηση του συνολικού κόστους της θεραπείας. Ωστόσο, στην πραγματική ζωή, είναι πιθανές καθυστερήσεις και εάν ο ασθενής φτάσει όταν δεν υπάρχει χώρος για να φιλοξενηθεί, θα πρέπει να μπει σε λίστα αναμονής μέχρι να ανοίξει μία θέση. Αυτό το βήμα είναι πολύ σημαντικό να απεικονιστεί στο μοντέλο, καθώς θα μειώσει σημαντικά το κόστος, κάτι που είναι ο κύριος τρέχων στόχος. Ο χρόνος αναμονής θα ληφθεί υπόψη μετά την είσοδο του ασθενούς στο νοσοκομείο της λευκαφαίρεσης και πριν από τη διαδικασία της λευκαφαίρεσης. Με αυτόν τον τρόπο, αποφεύγονται προβλήματα διάρκειας ζωής. Ωστόσο, ένας μέγιστος χρόνος αναμονής θα εφαρμοστεί ως περιορισμός, επειδή οι καρκινοπαθείς στα τελευταία στάδια δεν μπορούν να αντέξουν πολύ μεγάλες λίστες αναμονής.

Στη συνέχεια παρουσιάζονται τα αποτελέσματα για κάθε έναν από τους παραπάνω στόχους. Όσον αφορά την πολυκριτηριακή βελτιστοποίηση, συγκρίνοντας τις δύο μεθόδους, η epsilon constraint φαίνεται να είναι πιο αποτελεσματική αφού η κατανομή των λύσεων είναι πιο ομοιόμορφη και υπολογίζονται πολλά περισσότερα βέλτιστα σημεία pareto σε σύγκριση με τη μέθοδο του σταθμισμένου αθροίσματος. Η τελευταία, αν και πολύ απλή, δίνει αξιόπιστα αποτελέσματα, αλλά οι λύσεις ομαδοποιούνται γύρω από ορισμένα σημεία και δεν κατανέμονται ομοιόμορφα σε ολόκληρο τον χώρο των πιθανών αποφάσεων. Αυτό το πρόβλημα είναι εγγενές στη μέθοδο του σταθμισμένου αθροίσματος, καθώς τείνει να βρίσκει βέλτιστες λύσεις συγκεντρωμένες γύρω από ορισμένα σημεία. Άλλα μειονεκτήματα της μεθόδου περιλαμβάνουν: (1) το ομοιόμορφα κατανεμημένο σύνολο βαρών δεν εγγυάται ένα ομοιόμορφα κατανεμημένο σύνολο Pareto-βέλτιστων λύσεων, (2) Δύο διαφορετικά σετ βαρών δεν οδηγούν απαραίτητα σε δύο διαφορετικές Pareto-βέλτιστες λύσεις.

Στη δεύτερη ενότητα αποδεικνύεται πόσο σημαντικό είναι να μεγιστοποιηθεί η αξιοποίηση κάθε μονάδας παραγωγής για να ελαχιστοποιηθεί το κόστος. Αυτό επιτυγχάνεται με την κατανομή με βέλτιστο τρόπο των εισερχόμενων ασθενών στα διαφορετικά κέντρα λευκαφαίρεσης, για να επιτραπεί καλύτερος προγραμματισμός ασθενών στις εγκαταστάσεις παραγωγής. Και στα τρία διαφορετικά δίκτυα που δοκιμάστηκαν για τα τρία επίπεδα ζήτησης, αποδείχθηκε ότι το μέσο κόστος ανά θεραπεία μειώθηκε περισσότερο από 40% σε σύγκριση με τα αποτελέσματα του αρχικού μοντέλου. Για 50 ασθενείς το αρχικό μοντέλο προτείνει τη δημιουργία των εγκαταστάσεων m1 και m4 και η θεραπεία έχει μέσο κόστος 142,7 K$18, ενώ το νέο μοντέλο χρησιμοποιεί μόνο την εγκατάσταση m1 και το κόστος είναι 82,6 K$. Για 125 ασθενείς το αρχικό μοντέλο επιλέγει τις εγκαταστάσεις m3 και m6 με μέσο κόστος ανά θεραπεία στα 143,7k$ 18, ενώ το βελτιωμένο μοντέλο χρησιμοποιεί είτε τις

εγκαταστάσεις m1 και m4 είτε την m3 μόνο με κόστος περίπου 80,1k$. Αναφέρεται ότι ο μέσος χρόνος επιστροφής σε όλα τα σενάρια είναι περίπου 18 ημέρες. Επίσης, από την ανάλυση των δικτύων παρατηρήθηκε ότι ο πρώτος κόμβος που θα κορεστεί είναι οι εγκαταστάσεις παραγωγής. Επειδή η αγορά των θεραπειών με κύτταρα CAR-T είναι νέα και η ζήτηση μπορεί να είναι απροσδόκητη, προτείνεται ένας σχεδιασμός ασφαλείας 25% αυτής της μονάδας ώστε να είναι σε θέση να απορροφά πιθανές διακυμάνσεις ζήτησης. Με τον έλεγχο αυτής της υπόθεσης, παρατηρείται ότι η χωρητικότητα του μικρού δικτύου συνολικά αυξήθηκε κατά 17% και η χωρητικότητα του δικτύου μεσαίου μεγέθους κατά 30%. Επιπλέον, δοκιμάστηκαν εναλλακτικά δίκτυα ίδιας χωρητικότητας για να αξιολογηθεί η δυνατότητα ενοικίασης μέρους άλλων υφιστάμενων εγκαταστάσεων. Αυτή μπορεί να είναι μια βραχυπρόθεσμη λύση πριν αποφασιστεί ποιες εγκαταστάσεις θα δημιουργηθούν και με ποια χωρητικότητα ή μια μακροπρόθεσμη λύση όταν θα χρειαστεί επέκταση του δικτύου λόγω υψηλότερων απαιτήσεων. Παρατηρήθηκε ότι τα δίκτυα με μία μονάδα παραγωγής με μεγαλύτερη χωρητικότητα αποδίδουν ελαφρώς καλύτερα από τα πιο περίπλοκα δίκτυα με δύο ή τρεις εγκαταστάσεις με μικρότερη χωρητικότητα. Αυτό συμβαίνει επειδή υπολογιστικά το πρόβλημα γίνεται πιο δύσκολο όσο πιο περίπλοκο είναι το δίκτυο.

Τέλος, η προσθήκη του χρόνου αναμονής στο μοντέλο ήταν ένα πολύ σημαντικό βήμα, καθώς κάνει το δίκτυο πιο ρεαλιστικό και πολύ πιο οικονομικό, εισάγοντας την έννοια της συσσώρευσης. Είναι αλήθεια ότι η βέλτιστη κατανομή των ασθενών μπορεί να μην είναι πάντα δυνατή, καθώς οι θεραπείες απευθύνονται σε ασθενείς με καρκίνο στο τελικό στάδιο που δεν θα μπορούν να ταξιδέψουν. Για το λόγο αυτό, έχει εισαχθεί χρόνος αναμονής στο μοντέλο. Όταν η μονάδα παραγωγής γεμίσει και φτάσει ένας νέος ασθενής, μπαίνει αυτόματα σε λίστα αναμονής έως ότου ανοίξει μία γραμμή παραγωγής και ο ασθενής προχωρήσει στη λευκαφαίρεση. Και για τα δύο προφίλ ζήτησης που δοκιμάστηκαν το κόστος ήταν σχεδόν 40% χαμηλότερο σε σύγκριση με το αρχικό μοντέλο, καθώς οι υπάρχουσες εγκαταστάσεις παραγωγής χρησιμοποιήθηκαν πολύ αποδοτικότερα. Το κόστος μειώθηκε σε 81,6K$ και 82,5K$ για τα προφίλ ζήτησης 50 και 125 ασθενών αντίστοιχα. Αυτό που είναι επίσης πολύ σημαντικό είναι ότι ο χρόνος παράδοσης της θεραπείας δεν αυξήθηκε πολύ για τη συντριπτική πλειοψηφία των ασθενών. Αυτά τα ευρήματα υποδηλώνουν ότι το νέο μοντέλο είναι σημαντικά βελτιωμένο σε σύγκριση με το αρχικό.

Περιεχόμενα

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CHAPTER 1: LITERATURE REVIEW

1.1 SUPPLY CHAIN OPTIMIZATION

1.1.1 WHAT IS A SUPPLY CHAIN?

A supply chain is defined as a network of facilities that performs the functions of procurement of materials, transformation of these materials into intermediate and finished products, and distribution of these products to customers[27]. Supply chain organization is one of the core functions of a business because it ensures that products will reach final costumers and subsequently profitability will be achieved. A typical supply chain involves suppliers, production sites, storage facilities, and customers. Nevertheless, the management of such systems is quite complex due to the multiplicity of material and information flows, diversified characteristics of entities, and often-present contradicting objectives.[1]

The main objectives of designing an efficient supply chain include: (i) minimization of costs, delivery delays, inventories, and investment, (ii) maximization of deliveries, profit, return on investment (ROI), customer service level, and production. To succeed in these goals, location, production, inventory and transportation decisions need to be made. These involve: the number, size, and physical location of production plants, warehouses, and distribution centers, the products to be produced at each plant and the allocation of suppliers to plants, of plants to distribution centers, and of distribution centers to customers. The detailed production scheduling at each plant must also be decided. Moreover, management of the inventory levels and the transportation media to be used must be defined. [2]

In typical SCM problems, it is assumed that capacity, demand, and cost are known parameters. However, this is not the case in reality, as there are uncertainties arising from variations in customers' demand, supplies transportation, organizational risks and lead times. Demand uncertainties, in particular, has the greatest influence on SC performance with widespread effects on production scheduling, inventory planning, and transportation.[3]

Typical supply chain problems Supply chain problems may be divided into three categories: (i) supply chain infrastructure (network) design; (ii) supply chain analysis and policy formulation; (iii) supply chain planning and scheduling. The last involves deciding how to operate the network to respond best to the external conditions faced by the supply chain.[4]

1.1.2 WHY IS PROCESS SYSTEMS ENGINEERING IMPORTANT?

It is observed from paragraph 1.1.2 that supply chain management is very challenging and demanding and the need for computational tools able to assist decision making seems imperative.

Market and societal demands continue to increase and as a result modern supply chains must face new challenges. Some of them include shorter product life cycles, mass customization, personalized products and the need for more sustainable processes and products. [1,4].

The Process Systems Engineering (PSE) community can make an important contribution to address the challenges above through the development of tools that support the required process supply chain flexibility. Such contributions already exist and span from to tactical and operational problems. [1] The following table represents some of the milestone-papers as far as scheduling in chemical engineering is concerned.

Table 1: Representative papers on the evolution of scheduling in chemical engineering

Reference	**Output**
Reklaitis, G.V., 1978. [32]	Review of scheduling of process operations
Mauderli, A.M., Rippin, D.W.T., 1979. [33]	They search for alternative ways of producing one batch of each of the various products, choose alternative production lines to be constructed and set in parallel production lines of the same, or different products to form alternative campaign candidates
Shah, N., 1998. [34]	He gives an overview of single- and multisite planning and scheduling
Kallrath, J., 2002. [35]	Kallrath focuses on different types of scheduling problems and presents some

	solution approaches especially those applied to a benchmark problem.
Floudas, C.A., Lin, X., 2004. [36]	They classify existing approaches in scheduling based on the time representation and discuss important characteristics of chemical processes that pose challenges to the scheduling problem.
Maravelias, C.T., Sung, C., 2009. [37]	They review the integration of medium-term production planning and short-term scheduling and explain why integration with scheduling leads to better solutions.
Wassick, J., 2009. [38]	He discusses the nature of an integrated chemical production site to identify the opportunities for enterprise-wide optimization. He shows how the site is composed of sub-systems, which present several planning and operational challenges that can be optimized. Also, waste disposal scheduling is presented in detail.
Grossmann, I.E., 2012. [39]	He provides an overview of EWO in terms of a mathematical programming framework (mixed-integer linear and nonlinear optimization methods), as well as decomposition methods, stochastic programming and modeling systems. He also addresses some of the major issues involved in the modeling and solution of these problems and describe several applications to show the potential of this area.

Harjunkoski, I., Maravelias, C., Bongers, P., Castro, P.M., Engell, S., Grossmann, I.E., Hooker, J., Méndez, C., Sand, G., Wassick, J., 2014 [40]	They review scheduling methodologies developed for process industries. Above all, the aim of the paper is to focus on the industrial aspects of scheduling and discuss the main characteristics, including strengths and weaknesses of the presented approaches. Moreover, usability, interfacing and integration are discussed.
Baldea, M., Harjunkoski, I., 2014. [41]	They dentify key elements of control and scheduling, and carry out a systematic investigation of their use as building blocks for the formulation and solution of the integrated scheduling/control problem.
Dias, L.S., Ierapetritou, M., 2016. [42]	They analyze uncertainties in process scheduling and control, and describe the different mathematical approaches to describe and optimize problems under uncertainty.

1.3.3 MODEL-BASED METHODOLOGIES

Heuristic-Based Approaches. Williams [19] presents seven heuristic algorithms for scheduling production and distribution operations in supply chain networks, comparing them with each other and with a dynamic programming model. The objective is to determine a minimum cost production and product distribution schedule, satisfying the product demand, in a given distribution network. It is assumed that the demand rate is constant, and that processing is instantaneous, with no delivery lags between facilities. [5]

Mathematical Programming-Based Approaches. The alternative to heuristics is the use of mathematical models of supply chains. Optimization problems can be classified into the following categories:

Least-squares problems: A least squares problem is an optimization problem with no constraints and an objective which is a sum of squares of terms. The solution of least-squares problem can be reduced to analytically solving a set of linear equations. For least-squares problems there are good algorithms and software implementations for solving the problem to high accuracy, with very high reliability. Least-squares problems are the formulation of regression analysis, optimal control and many parameters estimation and data fitting methods such as clustering techniques. [6]

Linear programming (LP) is a type of convex programming and addresses problems with linear objective function and linearly formulated constraints. For LP there is not a characteristic analytical formula but there is a variety of methods such as Simplex method and interior point methods. LP is commonly examined in operations research for a variety of problems such as planning, routing, scheduling, assignment, and design.[6]

Mixed Integer programming (MILP) studies linear programs in which some variables are constrained to take only integer values. This type of programming is more difficult than regular linear programming. In many MILP cases integer variables are binary (0-1 variables). For every combination of binaries, a different optimization problem arises. The most common algorithms to address MILP are:

- Branch and bound methods, a binary tree is employed for the representation of the 0 — 1 combination, the feasible region is partitioned into subdomains systematically, and valid upper and lower bounds are generated at different levels of the binary tree.

- Cutting plane methods, the feasible region is not divided into subdomains but instead new constraints, denoted as cuts, are generated and added which reduce the feasible region until a 0 — 1 optimal solution is obtained.
- Decomposition methods, the mathematical structure of the models is exploited via variable partitioning, duality, and relaxation methods.
- Logic- based methods, disjunctive constraints or symbolic inference techniques are utilized which can be expressed in terms of binary variables

Non-Linear Programming studies the general case in which the objective function or the constraints or both are composed of nonlinear elements. This may or may not be a convex program. Pivoting and other algebraic procedures are commonly used by NLP algorithms to replace the original problem by an approximating linear one, these nonlinear algorithms renew the approximations of each iteration based on the solution of the last one. [7]

Quadratic programming (QP) examines problems whose objective function has quadratic terms, while the feasible set is specified with linear equalities and inequalities. Quadratic programming is the simplest case of NLP. [7]

Dynamic Programming is an optimization approach that transforms a complex problem into a sequence of simpler problems; its essential characteristic is the multistage nature of the optimization procedure.[8]

Stochastic programming problems have constraints or parameters depending on random variables. In contrast to deterministic optimization, real world problems almost invariably include parameters which are unknown at the time a decision should be made. When the parameters are uncertain but assumed to lie in some given set of possible values, one might seek a solution that is feasible for all possible parameter choices and optimizes a given objective function.

Robust optimization is, like stochastic programming, an attempt to capture uncertainty in the data underlying the optimization problem. Robust optimization aims to find solutions that are valid under all possible realizations of the uncertainties defined by an uncertainty set.

Table 2: Representative papers on the models used for supply chain scheduling

Reference	Model	Goal
Geoffrion and Graves [20]	MILP, which is solved using Benders decomposition	Design of a distribution system with optimal location of the intermediate distribution facilities between plants and customers, while minimizing the total distribution cost
Williams [21]	Dynamic programming algorithm	Determination of production and distribution batch sizes at each node within a supply chain network, while minimizing average cost
Brown et al. [22]	Optimization-based algorithm	Decision support system to manage complex problems involving facility selection, equipment location and utilization, and manufacture and distribution of products
Cohen and Lee [23]	MINLP	Maximization of the total after-tax profit for the manufacturing facilities and distribution centers
Newhart et al. [24]	Combination of mathematical programming and heuristic models	Minimization of the number of product types held in inventory throughout the supply chain
Pooley [25]	MILP	Minimization of the total operating cost of a production and distribution network.

Pirkul and Jayarama [26]	MILP, use of lagrangian relaxation	Study of a tri-echelon multicommodity system concerning production, transportation, and distribution planning, while minimizing establishing and operating cost.

It is observed that the majority of the supply chain problems are formulated as MILP models, since the description of supply chains relies largely on simple input-output models. Furthermore, while initially models are formulated as being deterministic, there often exists the need to account for uncertainties, ranging from demand uncertainty and equipment availability in scheduling settings to prices. Problems of the former type are often addressed through robust optimization techniques, since their goal is to ensure feasibility over a range of possible realization for the near-term future. In contrast, for long-term strategic problems, stochastic programming is often used because of its probabilistic view of the future and its focus on optimizing outcomes in expectation. Finally, it is worth recognizing that such problems are also often posed as multi-objective optimization problems, given potential conflicting objectives such as economics and customer satisfaction.[9]

Global Optimality

When talking about optimization models, a very important concept that arises is that of optimality. Ideally, global optimality is expected. Global optimality refers to an operating point which is the best possible over the entire domain with respect to some objective. It is true that not all problems can be addressed to optimality. The effectiveness of algorithms to reach global optimality varies with the form of the objective and constraints, the number of variables and constraints, and special structure of the problem, such as sparsity (the objective function depends on a small number of variables). Even if the objective function and constraints are smooth functions, e.g., polynomials, the optimization problem can be still difficult to solve not guarantying an optimum and requiring long computational time. Famous optimization problems such as the traveling salesman problem, the knapsack problem, scheduling problems, protein folding, and chemical equilibrium problems are global optimization problems. [10] If globally optimality cannot be reached, it is possible that local optimality can be achieved. A local optimum of an optimization problem is a solution that is

optimal within a neighboring set of candidate solutions. This is in contrast to a global optimum, which is the optimal solution among all possible solutions, not just those in a particular neighborhood of values.[10]

Solvers

Another important element involved in mathematical modelling and programming is the solvers that are used. In this thesis CPLEX is used. The name CPLEX itself is a word game built on the concept of a simplex algorithm written in C. CPLEX has evolved over time to adopt and become a leader in linear programming categories, such as integer programming, mixed integer programming and quadratic programming. In general optimization solvers help improve decision-making around planning, allocating and scheduling scarce resources. They embed powerful algorithms that can solve mathematical programming models, constraint programming and constraint-based scheduling models.

1.2 CAR-T CELL THERAPIES

1.2.1 WHAT ARE THEY, HOW ARE THEY PRODUCED?

CAR-T cell therapy is a novel and potent immunotherapy-based technique with encouraging results in the treatment of cancer. Such therapies utilize the patients own immune system to target and fight cancer. [11]

The immune system is the body's defense against infection and cancer. It is made up of billions of cells that are divided into several different types. Lymphocytes, a subtype of white blood cells, comprise a major portion of the immune system. There are three types of lymphocytes:

- B lymphocytes (B cells) make antibodies to fight infection.
- T lymphocytes (T cells) have several functions, including helping B lymphocytes to make antibodies to fight infection, and directly killing infected cells in the body.
- Natural killer cells also attack infected cells and eliminate viruses.

Immune cells or antibodies can be produced in the laboratory under tightly controlled conditions and then given to patients to treat cancer. Several types of immunotherapies are either approved for use or are under study in clinical trials to determine their effectiveness in treating various types of cancer. [12]

T-cells although efficient in fighting infection, cannot easily recognize cancer cells and thus the latter evade immune response and continue to develop the cancer. Scientist are working towards the introduction of the Chimeric Antigen Receptor to the T cells to enhance their targeting at cancer cells. These CAR T-cells are designed to recognize and target a specific protein on the cancer cells. [13]

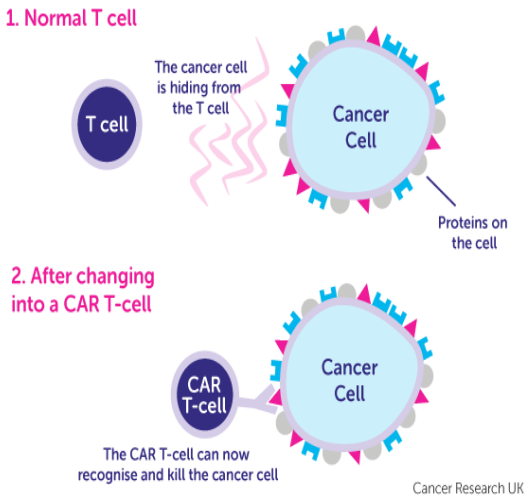

Figure 1: Normal T-Cells vs Engineered T-Cell[31]

Chimeric antigen receptor CAR structure. A CAR molecule comprises an extracellular MHC-independent antigen-binding ectodomain derived from a monoclonal antibody, including a single chain variable fragment (scFV), a linker, and a spacer/hinge region, a transmembrane domain, and an intracellular T cell signaling endodomain. [14]

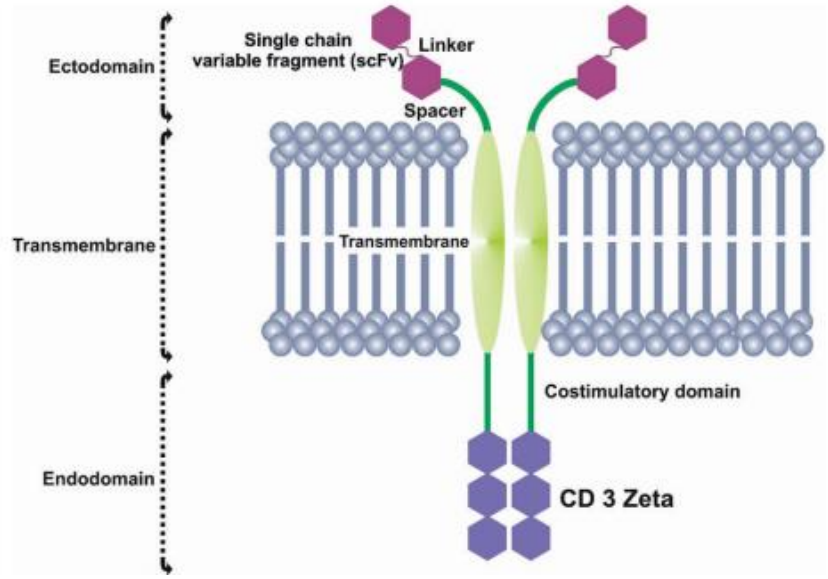

Figure 2: Chimeric Antigen Receptor Structure[5]

Autologous CAR-T cell manufacturing

The first step in the process is the leukapheresis, where T-cells are extracted from patient's blood. Disease, advanced age, prior therapy, and peripheral blood characteristics (lymphopenia, high peripheral disease burden) can lead to compromised quality or quantity of CAR-T cells in the final product. Cell enrichment follows. This can be done using elimination techniques (density gradient, counter flow elutriation, flask adherence techniques) or cell selection techniques (antibody fluorochrome conjugates, antibody-magnetic bead conjugates, heptamer-based isolation methods). The third step is cell simulation and activation which depends on the type of stimulatory reagents and the duration of activation. After that CAR gene transfer occurs. This can happen using viral systems (γ-retroviral vectors, lentiviral vectors) or non-viral systems (electroporation, targeted insertion strategies such as zinc finger nuclease, transcription activator-like effector nucleases, CRISPR-CAS9). Cell expansion follows. During this step reagents, supplemented with cytokines to enhance ex-vivo CAR-T cell proliferation, are used in the culture media. Cytokines type and doses can severely affect product quality. Also, duration of culture should be monitored as more culture days

lead to more differentiation and less tumor killing capacity. Expansion can be executed in bioreactors or culture platforms. Specifically, flask systems, closed system bags, partially and fully automated systems (CliniMACs prodigy, Cocoon). The last step involves cryopreservation and thawing of the final product, where the type and concentration of cryoprotectant, the method of freezing, the storage conditions and the method, duration and rate of thawing must be determined.

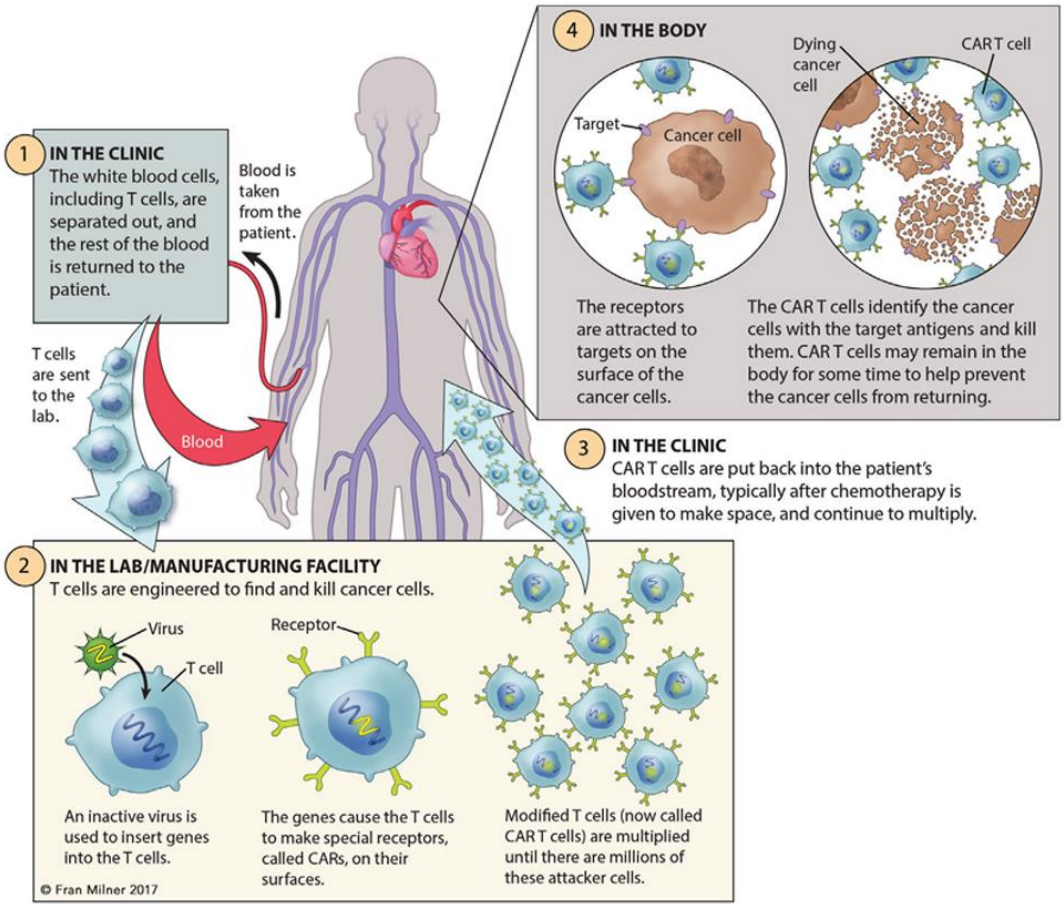

Figure 3: Autologous CAR-T cell process[12]

FDA Approved therapies

The US Food and Drug Administration (FDA) in 2017 and the European Medicines Agency (EMA) in 2018 approved KYMRIAHTM of Novartis, the first autologous CD19- specific CAR T cell therapy. Subsequently, YESCARTATM of Kite Pharma was the second CAR T cell therapy to be approved by FDA and EMA in 2017 and 2018 respectively. Finally, TECARTUSTM, another cell-based immunotherapy from Kite Pharma, and BREYANZITM from Bristol Myers Squibb granted approval from FDA in July 2020 and February 2021 respectively.[15]

Critical quality attributes

- Safety: negative sterility test and lack of oncogenic or viral replicative potential
- Purity: High concentration of CAR-T cells minimal contaminating cells
- Consistency: Meet lot release criteria time after time
- Potency: Capability to eliminate tumor cells
- Durability: Persistence in circulation, ability to maintain its anti-tumor effects

CAR-T cell therapies price

The US list price for the approved therapies varies between $373,000 and $475,000. The high prices of these therapies reflect the benefit they deliver as well as the impact associated with manufacturing, distribution and product administration.[30] Time-intensive manufacturing processes, in-time delivery under hospital admission and daily monitoring of the patient for side effects are among the factors that increase the cost.

1.2.2 SUPPLY CHAIN OF CAR-T CELL THERAPIES

The main steps of a typical CAR T cell therapy lifecycle are: (a) patient identification, (b) leukapheresis, (c) manufacturing, (d) Quality Control, (e) therapy administration.

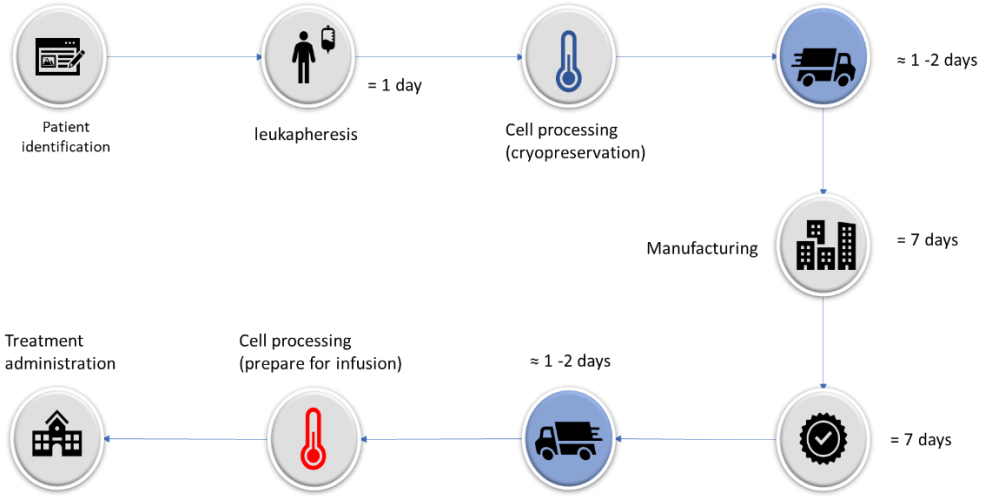

Figure 4: Supply Chain of CAR-T cell therapies

Patient identification involves tracking and control of each patient's product from leukapheresis to infusion, ensuring the safe delivery of the right therapy to the right patient[16]. The first step to the CAR T cell treatment is the collection of peripheral blood mononuclear cells (PBMC) from the patient (autologous) or a donor (allogeneic) by leukapheresis, a method that separates the leukocytes from the blood. 4. This process takes place in specialized clinical centers. Next, within 24h after collection, the leukapheresis material undergoes a freezing process and it is shipped, either fresh at -80 °C or cryopreserved at -120 °C, to the manufacturing site, where it might be stored before it is further processed 25,35 Cryopreserved. [29] leukapheresis is preferred over fresh because it offers maximum flexibility in the supply chain management, as it enables extended storage in case of manufacturing delays and time flexibility for patients undergoing the procedure [16,29]. The manufacturing process follows as described above. After the completion of the manufacturing process, Quality Control takes place. The final product undergoes testing of critical quality attributes (CQAs), which can be conducted either in the manufacturing site or in a different facility. Finally, the cryopreserved CAR T cell therapy is transported to the clinical site. Before the administration of the CAR T cell therapy, the patient must be treated with lymphodepleting chemotherapy. Once the pre-conditioning that can last up to 1-week finishes, the cells are thawed and immediately infused to the patient [16]. After the administration, patients are closely monitored for side effects related to the therapy such as cytokine release syndrome and neurotoxicity [14].

It is evident that CAR T cell therapy targets are expanding rapidly, with scientific interest and clinical trials in autoimmune diseases, viral infections (HIV and SARSCoV-2), allergies, and asthma. Currently, there are 6,581 active and ongoing clinical trials regarding CAR T cell treatments, with most of them being autologous, while their allogeneic counterpart is progressing as well.

Apart from cost minimization, delivery time of therapies is a pressing factor that must be taken into consideration when designing the supply chain. In commercial treatments turnaround time varies between 15-24 days [28].

From the above it is obvious that digital tools such as mathematical modelling can assist in decision making and identification of optimal network structures that will ensure minimized cost and delivery time of the therapies.

1.3 MULTI-OBJECTIVE OPTIMIZATION

Optimization aims to find the best solution that minimizes the objective function by changing design variables while satisfying certain constraints. During design optimization several design criteria and multiple objective functions have to be considered at the same time. For example, in the case of CAR-T cel therapies, cost must and return time must be minimized. When more than one objective is optimized, the optimization becomes multiobjective, in which case the usual design optimization for a scalar objective function cannot be used.(Kim and de Weck)

Multi-objective optimization is an integral part of optimization problems and has vast applications, since almost all real-life optimization problems are described by numerous conflicting objectives. The process of optimizing systematically and simultaneously a collection of objective functions is called multi-objective optimization (MOO), [18].

The general multi-objective optimization problem is posed as follows:

$$\text{Min/max } f_m(x) \text{ , } m=1,2,3\ldots m$$

$$\text{Subject to } g_j(x) \geq 0,\ j=1,2,3\ldots j$$

$$h_k(x) = 0,\ k=1,2,3\ldots k$$

where m is the number of objective functions, j is the number of inequality constraints, and k is the number of equality constraints.

In contrast to single-objective optimization, in multi-objective optimization typically, there is no single global solution, and it is often necessary to determine a set of points that all fit a predetermined definition for an optimum. The predominant concept in defining an optimal point is that of Pareto optimality, which is defined as follows: Pareto Optimal: A point, $x* \in X$, is Pareto optimal if there does not exist another point, $x \in X$, such that $F(x) \leq F(x*)$, and $Fi(x) < Fi(x*)$ for at least one function. [19]

In simpler words, in the single-objective optimization problem, the superiority of a solution over other solutions is easily determined by comparing their objective function values. In multi-objective optimization problem, the suitability of a solution is determined by the dominance. For example, x_1 dominates x_2, if Solution x1 is no worse than x_2 in all objectives or Solution x_1 is strictly better than x_2 in at least one objective. [20] Koski [21] applied the weighted sum method to structural optimization. Marglin developed the ε -constraint method, and Lin developed the equality constraint method. Heuristic methods are also used for multiobjective optimization: Suppapitnarm applied simulated annealing to multiobjective optimization, and

multiobjective optimization by Genetic Algorithms can be found in Goldberg, and Fonseca and Fleming among others.

1.3.1 PARETO FRONTIER

Given a set of solutions, the non-dominated solution set is a set of all the solutions that are not dominated by any member of the solution set. The non-dominated set of the entire feasible decision space is called the Pareto-optimal set. The boundary defined by the set of all point mapped from the Pareto optimal set is called the Pareto optimal frontier.

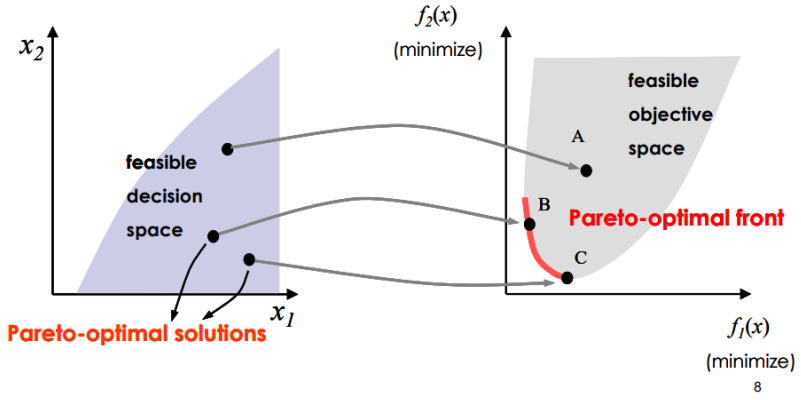

Figure 5: The pareto Optimal Frontier

1.3.2 WEIGHTED SUM METHOD

Stadler applied the notion of Pareto optimality to the fields of engineering and science in the 1970s. The most widely-used method for multiobjective optimization is the weighted sum method. The method transforms multiple objectives into an aggregated objective function by multiplying each objective function by a weighting factor and summing up all weighted objective functions. If $\sum_{i=1}^{m} w_i = 1 \; and \; 0 \leq w_i \leq 1$, the weighted sum is said to be a convex combination of objectives. Each single objective optimization determines one particular optimal solution point on the Pareto front. The weighted sum method then changes weights systemically, and each different single objective optimization determines a different optimal solution. The solutions obtained approximate the Pareto front. [17].

The weighted-sum method, as it is already mentioned, scalarizes a set of objectives into a single objective by pre-multiplying each objective with a user-supplied weight. This method is the simplest approach and is probably the most widely used classical approach. [19] Although the idea is simple, it poses the burden of choosing the suitable weights. Of course, there is not a unique answer, but rather it depends on the importance of each objective in the context of the problem. Generally, the relative value of the weights reflects the relative importance of the objectives. [18] By changing the weight vector, a different Pareto-optimal point can be obtained.

The weighted sum method is defined as follows:

$$\text{Minimize } \sum_{m=1}^{M} w_m \, f_m(x)$$

$$\text{Subject to } g_j(x) \geq 0, \; j=1,2,3\ldots j$$

$$h_k(x) = 0, \; k=1,2,3\ldots k$$

$$X_i^{(L)} \leq X_i \leq X_i^{(U)} \quad , \; i=1,2,3\ldots n$$

The most prominent advantage of this method is that it is quite simple. However, it also presents a series of disadvantages: first, It is difficult to set the weight vectors to obtain a Pareto-optimal solution in a desired region in the objective space. Second, it cannot find certain Pareto-optimal solutions in the case of a nonconvex objective space. Third, varying the weights consistently and continuously may not necessarily result in an even distribution of Pareto optimal points and an accurate, complete representation of the Pareto optimal set. [20]

1.3.3 ε-CONSTRAINT METHOD

In the epsilon constraint method, only one of the objectives is considered, while the rest are restricted within user-specified values. The modified problem is as follows:

$$\text{Minimize } f_{\mu}(x)$$

$$\text{Subject to } f_m(x) \leq \varepsilon_m \quad m=1,2,3\ldots m \text{ and } m \neq \mu$$

$$g_j(x) \geq 0,\ j=1,2,3\ldots j$$

$$h_k(x) = 0,\ k=1,2,3\ldots k$$

$$X_i^{(L)} \leq X_i \leq X_i^{(U)} \quad ,\ i=1,2,3\ldots n$$

In the above formulation, the parameter ε_m represents an upper bound of the value of f_m and need not necessarily mean a small value close to zero. [18]

One advantage of the method is that it is applicable to either convex or non-convex problems. One of the difficulties of this method is that the solution to the problem largely depends on the chosen ε vector. Also, the ε vector must be chosen carefully so that it is within the minimum or maximum values of the individual objective function. [20]

CHAPTER 2: PROBLEM DISCRIPTION AND BACKGROUND

2.1 OVERVIEW OF THE SUPPLY CHAIN NETWORK

The model examined in this work is a mixed integer linear programming (MILP) model that describes the CAR T cell supply chain, and it is used for the identification of the optimal supply chain network structure for the safe and in-time delivery of the therapies. The original model was developed by the lab of Professor Papathanasiou at Imperial College London[18] . The supply chain network includes 4 nodes: leukapheresis site, manufacturing site, Quality Control, and hospital.

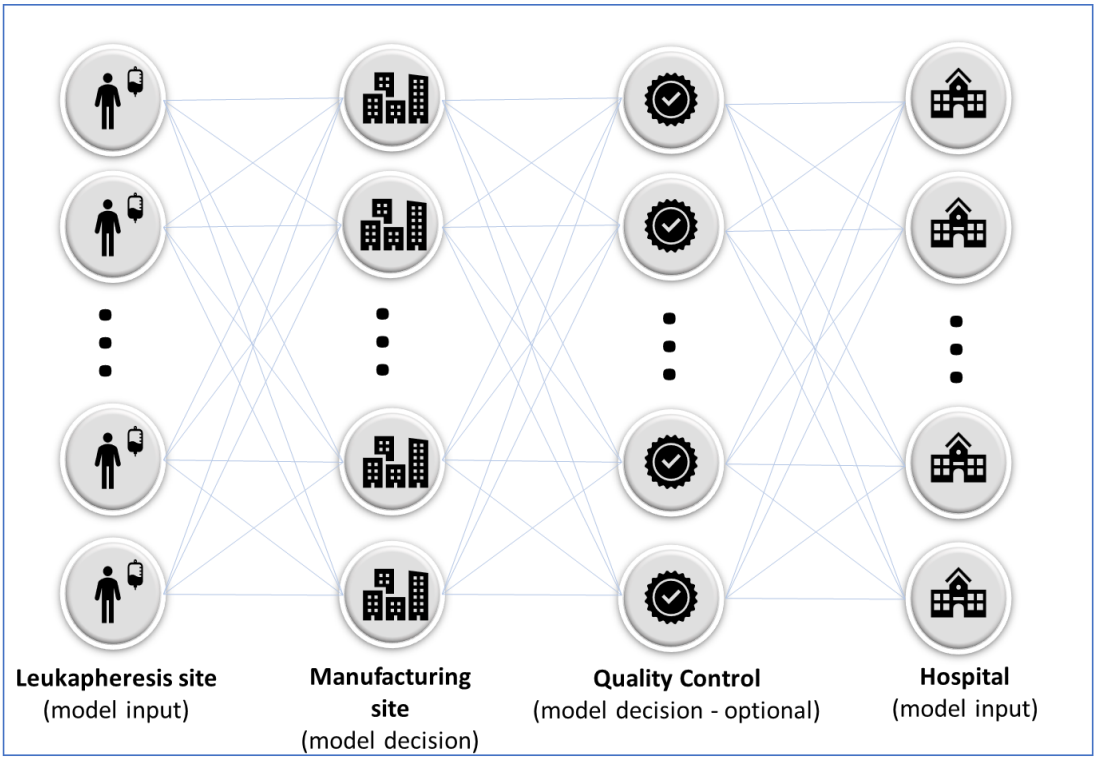

Figure 6: Overview of CAR-T cell therapy supply chain network

More specifically, a patient is allocated to a specialized leukapheresis site, where T cells are isolated from the bloodstream. Then, the cells are cryopreserved and transferred to the manufacturing facility. After cell processing and expansion, the final therapy undergoes a quality control check. In the model discussed quality control site is co-located with the manufacturing facility. If CAR-T cell successfully pass the control they are cryopreserved and

are transferred back to the hospital where they will be administered back to the patient. It should be mentioned that the hospital is co-located with the leukapheresis site. The objective of the model is to minimize the total cost of the therapies under certain given constraints.

In the single objective model[18], the network's performance is assessed for different demand scenarios (20,50,125 patients per 130 days) and different delivery times (17, 18, and 19 days). At this point, demand profiles are generated by an in-house algorithm and cost coefficients are assumed to be deterministic. Because the market of CAR-T cell is very new cost parameters have a 20% uncertainty. The study takes into account 4 leukapheresis sites and 4 hospitals in the UK and 6 manufacturing sites in the UK and Europe. The capacity and the location of the different manufacturing facilities are shown in the table below. Manufacturing time has been set to be 7 days.

Table 3: Capacity and location of manufacturing facilities

Manufacturing Facility	**# Panel Lines**	**Location**
M1	4	Stevenage (UK)
M2	31	Glasgow
M3	10	Berlin
M4	4	Belgium
M5	31	Pennsylvania
M6	10	Virginia

Inputs for the model include:

- A set of patients, P.
- A set of leukapheresis sites, C.
- A set of potential manufacturing sites, M.
- A set of transport modes, J.
- A set of time periods, T.

The model determines the:

- number and the location of the manufacturing facilities to be established.

• assignment and sequence of therapies to the manufacturing facilities at each time period.

• scheduling in the manufacturing sites.

• transport modes for the connection of the manufacturing sites with the leukapheresis sites and hospitals respectively.

2.2 DESCRIPTION OF THE ORIGINAL SINGLE-OBJECTIVE MODEL

The original mathematical model, on which this thesis is based, was developed by Professor Papathanasiou and her lab at Imperial College London[18].

The initial mathematical model of the CAR T cell supply chain and the corresponding nomenclature are displayed below.

Table 4: Nomenclature

Nomenclature	
Indices	
c	*Leukapheresis sites*
h	*Hospitals*
j	*Transport modes*
m	*Manufacturing sites*
p	*Patients*
t	*Time points Parameters*
TOTCOST	*Total cost of all the therapies p*
CMI_m	*Capital investment for manufacturing facility m*
CQC_p	*QC cost when in house*
CVM_m	*Fixed variable cost for manufacturing facility m*
$TT1_j$	*Transport time from leukapheresis to manufacturing site via transport mode j*
$TT2_j$	*Transport time from manufacturing site m to hospital h via transport mode j*

$U1_{m,h,j}$	*Unit transport cost from leukapheresis site c to manufacturing site m via transport mode j*
$U2_{m,h,j}$	*Unit transport cost from manufacturing site m to hospital h via transport mode j*
$FCAP_m$	*Total capacity of manufacturing facility m*
$INC_{p,c,t}$	*Demand therapy p arriving for leukapheresis c at time t*
$FMIN$	*Minimum flow*
$FMAX$	*Maximum flow*
NP	*Number of therapies*
NT	*Number of time points*
TLS	*Duration of leukapheresis*
$TMFE$	*Duration of manufacturing excluding QC*
TAD	*Duration of administration Variables*
$CTMp$	*Total manufacturing cost of therapy p*
$TTCp$	*Total transport cost per therapy p*
$OUTC_{p,c,t+TLS}$	*Therapy p leaving leukapheresis site c at time t*
$LSR_{p,c,m,j,t}$	*Therapy p that is leaving leukapheresis site c and is transported to manufacturing site m via transport mode j at time t*
$LSA_{p,c,m,j,t+TT1j}$	*Therapy p that left leukapheresis site c arriving at manufacturing site m via transport mode j at time t*
$INM_{p,m,t}$	*Therapy p arriving at manufacturing site m at time t*
$OUTM_{p,m,t+TMFE}$	*Therapy p leaving manufacturing site m at time t*
$MSO_{p,m,q,j,t}$	*Therapy p leaving manufacturing site m and is transported to hospital h via transport mode j at time t*

$FTD_{p,m,h,j,t}$	*Final therapy that left from manufacturing site m arriving at hospital h via transport mode j at time t*
$INH_{p,h,t}$	*Therapy p arriving at hospital h at time t*
$DURM_{p,m,t}$	*1 only for the time points t at which a therapy p is manufactured in facility m*
$RATIO_{m,t}$	*Percentage of utilization of manufacturing site m at time t*
$CAP_{m,t}$	*Capacity of manufacturing facility m at time t*
STT_p	*Starting time of treatment for patient p*
CTT_p	*Completion time of treatment for patient p*
TRT_p	*Total return time of therapy p*
$ATRT_p$	*Average return time of all the therapies p*
$E1_m$	*Binary variable to denote if manufacturing facility m is established*
$X1_{c,m}$	*Binary variable to denote if a match between leukapheresis site c and manufacturing facility m is established*
$X2_{m,h}$	*Binary variable to denote if a match between manufacturing facility m and hospital h is established*
$Y1_{p,c,m,j,t}$	*Binary variable to denote if sample p is transferred from leukapheresis site c to manufacturing facility m via transport mode j at time t*
$Y2_{p,m,h,j,t}$	*Binary variable to denote if sample p is transferred from manufacturing facility m to hospital h via transport mode j at time t*

Objective function.

The objective function of the single objective model minimizes the total cumulative cost of all manufactured CAR T cell therapies (Eq. A.1).

- $min\ TOTCOST = \sum_p CTM_p + \sum_p TTC_p + \sum_p CQC_p$ (A.1)

Equation (A.2) gives the manufacturing cost per therapy p.

- $CTM_p = NT \times \sum_m (E1_m \times (CIM_m + CVM_m)) / NP\ ,\ \forall\ p$ (A.2)

Equation (A.3) calculates the percentage of utilization of facility m at time t.

- $RATIO_{m,t} = \sum_p DURM_{p,m,t}\ FCAP_m\ ,\ \forall\ m,t$ (A.3)

The total cost for the transport of all therapies p from leukapheresis to manufacturing and from manufacturing to hospital is given by Equation (A.4).

- $TTC_p = \sum_{c,m,j,t} Y1_{p,c,m,j,t} \times U1_{c,m,j} + \sum_{m,h,j,t} Y2_{p,m,h,j,t} \times U2_{m,h,j}\ ,\ \forall\ p$ (A.4)

Material balances

Equation (A.5) represents the patient samples p collected at the leukapheresis site c at time t that are ready to be shipped to the manufacturing site m after the completion of the leukapheresis procedure:

- $INC_{p,c,t} = OUTC_{p,c,t} + TLS\ ,\ \forall p,\ c,t$ (A.5)

The patient samples p collected at the leukapheresis site c and are being shipped to manufacturing site m via transport mode j at time t will enter manufacturing after the duration of the transport (Eq. A.6).

- $LSR_{p,c,m,j,t} = LSA_{p,c,m,j,t+TT1j}\ ,\ \forall p,\ c,\ m,j,t$ (A.6)

Equation (A.7) displays the samples leaving leukapheresis site c at time t that are equal to patient samples p sent to all manufacturing sites m under transport mode j at time t.

- $OUTC_{p,c,t} = \sum_{m,j} LSR_{p,c,m,j,t\ m,j}\ ,\ \forall p,\ c,t$ (A.7)

Patient sample p entering manufacturing site m at time t is equal to patient samples p shipped from all leukapheresis sites c to manufacturing facility m (Eq. A.8).

- $INM_{p,m,t} = \sum_{c,j} LSA_{p,c,m,j,t\ c,j}\ ,\ \forall p,\ m,t$ (A.8)

The outgoing therapy p of manufacturing site m at time t will be ready to be shipped after the manufacturing process and quality control have finished (Eq. A.9).

- $INM_{p,m,t} = OUTM_{p,m,t+TMFE+TQC}, \forall p, m, t$ (A.9)

The therapy p leaving manufacturing site m at time t is equal to the therapy ready to be transferred to a hospital h via transport mode j (Eq. A.10).

- $OUTM_{p,m,t} = \sum_{h,j} MSO_{p,m,h,j,t}, \forall p, m, t$ (A.10)

Therapy p that has left manufacturing site m enters hospital h under transport mode j at time t after the duration of transport under transport mode j (Eq. A.11).

- $FTD_{p,m,h,j,t} = MSO_{p,m,h,j,t+TT2j}, \forall p, m, h, j, t$ (A.11)

Equation (A.12) gives the therapy p that arrives at hospital h at time t.

- $INH_{p,h,t} = \sum_{m,j} FTD_{p,m,h,j,t}, \forall p, h, t$ (A.12)

Capacity constraints.

Equation (A.13) gives the capacity of each manufacturing site m at every time t, whilst Equation (A.14) makes sure that the therapies do not exceed the available capacity of each manufacturing site.

- $CAP_{m,t} = FCAP_m - \sum_p INM_{p,m,t}, \forall p, m, t$ (A.13)
- $\sum_p INM_{p,m,t} - \sum_p OUTM_{p,m,,t} \leq CAP_{m,t}, \forall p, m, t$ (A.14)

Network structure constraints.

Equations (A.15)-(A.16) ensure that matches are only made with existing manufacturing facilities.

- $X1_{c,m} \leq E1_m, \forall c, m$ (A.15)
- $X2_{m,h} \leq E1_m, \forall c, m$ (A.16)

Equations (A.17)-(A.18) ensure that only one transport mode j can be selected for each therapy p at every journey.

- $\sum_{c,m,j,t} Y1_{p,c,m,j,t} \leq 1, \forall p, c, m, j, t$ (A.17)
- $\sum_{m,h,j,t} Y2_{p,m,h,j,t} \leq 1, \forall p, m, h, j, t$ (A.18)

Equations (A.19)-(A.22) make sure that a match is only made between a leukapheresis site c and its corresponding co-located hospital h.

- $\sum_{m,j,t} Y2_{p,m,h1,j,t} \leq \sum_{t} INC_{p,c1,t} \times t \ , \forall p$ (A.19)
- $\sum_{m,j,t} Y2_{p,m,h2,j,t} \leq \sum_{t} INC_{p,c2,t} \times t \ , \forall p$ (A.20)
- $\sum_{m,j,t} Y2_{p,m,h3,j,t} \leq \sum_{t} INC_{p,c3,t} \times \ t \ , \forall p$ (A.21)
- $\sum_{m,j,t} Y2_{p,m,h4,j,t} \leq \sum_{t} INC_{p,c4,t} \times t \ , \forall p$ (A.22)

Demand satisfaction.

Equation (A.23) ensures that the total rate of flow of every therapy p arriving at hospital h is equal to the corresponding demand. Logical constraints for transportation flows.

- $\sum_{p,h,t} INH_{p,h,t} = NP, \forall p, h,t$ (A.23)

Inequalities (A.24) and (A.25) state that a therapy p can be transferred from a leukapheresis site c to a manufacturing site m and from a manufacturing site m to a hospital h if and only if a match between the corresponding facilities has been previously made.

- $Y1_{p,c,m,j,t} \leq X1_{c,m}, \forall p, c, m,j,t$ (A.24)
- $Y2_{p,m,h,j,t} \leq X2_{m,h}, \forall p, m, q,j,t$ (A.25)

Equations (A.26)-(A.29) confirm that a minimum and maximum flow of material exists for a transportation link to be established.

- $LSR_{p,c,m,j,t} \geq Y1_{p,c,m,j,t} \times FMIN, \forall p, c, m,j,t$ (A.26)
- $LSR_{p,c,m,j,t} \leq Y1_{p,c,m,j,t} \times FMAX, \forall p, c, m,j,t$ (A.27)
- $MSO_{p,m,hj,t} \geq Y2_{p,m,h,j,t} \times FMIN, \forall p, m, h,j,t$ (A.28)
- $MSO_{p,m,hj,t} \leq Y2_{p,m,h,j,t} \times FMAX, \forall p, m, h,j,t$ (A.29)

Time constraints.

Equation (A.30) calculates the manufacturing time t of therapy p in facility m.

- $DURM_{p,m,t} = \sum_{t} INM_{p,m,t-1} - \sum_{t} OUTM_{p,m,t} + OUTM_{p,m,t} \ , \forall \ p, m,t$ (A.30)

Equation (A.31) gives the time point when a patient checks into a leukapheresis site c.

- $STT_p = \sum_{c,t} INC_{p,c,t} \times t, \forall p$ (A.31)

Equation (A.32) displays the time point, when therapy p is delivered to the hospital h.

- $CTT_p = \sum_{h,t} INH_{p,h,t} \times t \ , \forall p$ (A.32)

Constraint (A.33) makes sure that the time point a patient checks into a leukapheresis site c chronologically precedes the time point the corresponding therapy p is delivered to the hospital h.

- $STT_p \leq CTT_p, \forall p$ (A.33)

Equation (A.34) presents the total time for a therapy p from the time point the patient checks into a leukapheresis site c until the time point that the therapy is safely delivered to the hospital h.

- $TRT_p = CTT_p - STT_p, \forall p$ (A.34)

Inequality (A.35) ensures that the turnaround of a therapy p is less than or equal to 18 days. This constraint can change to 17, 18, or 19 days depending on the specific case examined.

- $TRT_p \leq 18$ (A.35)

Equation (A.36) calculates the average return time of all the therapies p.

- $ATRT_p = \sum_p TRT_p / NP$ (A.36)

Equation (A.37) calculates the total cost per therapy

- $\mathrm{TCPT_p} = \mathrm{CTM_p} + \mathrm{TTC_p} + 10476 + 9312$ (A.37)

2.3 ORIGINAL SINGLE OBJECTIVE MODEL - RESULTS

In this section the results of the single objective optimization will be presented. They consist base scenarios developed by the lab of Professor Papathanasioiu to which future results and analysis will be compared to, in order to identify improvements[18].

Three different demand scenarios (20, 50, 125 patients/ 130 days) and three turnaround times (17, 18 and 19 days) are evaluated:

Table 5: Established facilities, total cost and total return time – single objective model – demand levels (20, 50 ,125)

# SCENARIO	Demand profiles	Delivery time	Total Cost (M $)	Cost/ therapy (K $)	Established manufacturing facilities
1	20 patients	17	3,48	174,1	m1
2		18	3,45	172,6	m1
3		19	3,43	171,6	m1
4	50 patients	17	7,22	144,4	m1, m4
5		18	7,14	142,7	m1, m4
6		19	7,09	141,8	m1, m4
7	125 patients	17	18,23	145,8	m3, m6
8		18	17,97	143,7	m3, m6
9		19	17,83	142,6	m3, m6

As it was expected, for all three demand profiles the total cost of therapies increases as the delivery time decreases. This is because the fastest and most expensive transportation mode is employed. To better depict this tradeoff between time and cost, it is useful to design a new model able to optimize the two objectives simultaneously. This is presented in paragraph 4.2.

Moreover, it is observed that the cost per therapy decreases when the number of patients goes from 20 to 50 but increases a bit when the number increases to 125 from 50. Personalized therapies are not typically economies of scale, so the fact that the cost/ per therapy increases as the number of patients increases it is not surprising at a first glance. However, the capacity utilization must be checked for each scenario to ensure that the

proposed network is fully utilized, and the cost is minimized. It is true that if the ratio of utilization is high, the variable cost of production decreases, and this is reflected on the total price.

Table 6: Capacity Utilization – Scenaria 1-9

# SCENARIO	Demand profiles	Delivery time	AVERAGE UTILIZATION RATIO (%)
1	20 patients	17	m1: 26.9%
2		18	m1: 26.9%
3		19	m1: 26.9%
4	50 patients	17	m1: 53.9%
			m4: 13.5%
5		18	m1: 56.5%
			m4: 10.8%
6		19	m1: 55.2%
			m4: 12.1%
7	125 patients	17	m3: 58.2%
			m6: 9.2%
8		18	m3: 57.6%
			m6: 9.7%
9		19	m3: 57.6%
			m6: 9.7%

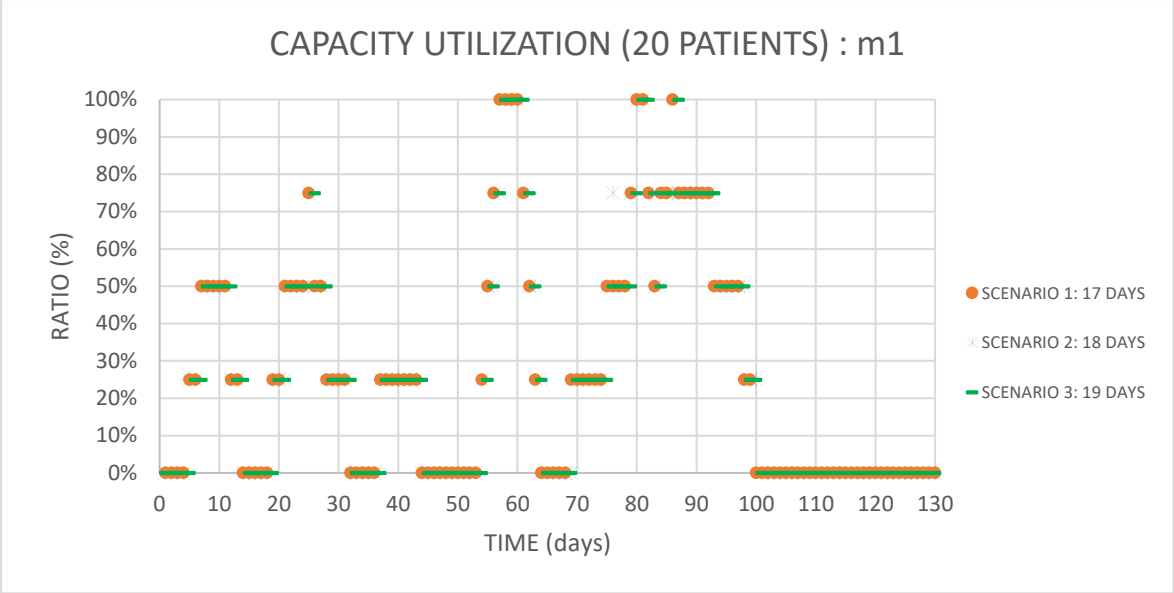

Figure 7: Capacity utilization of m1 for 20 patients

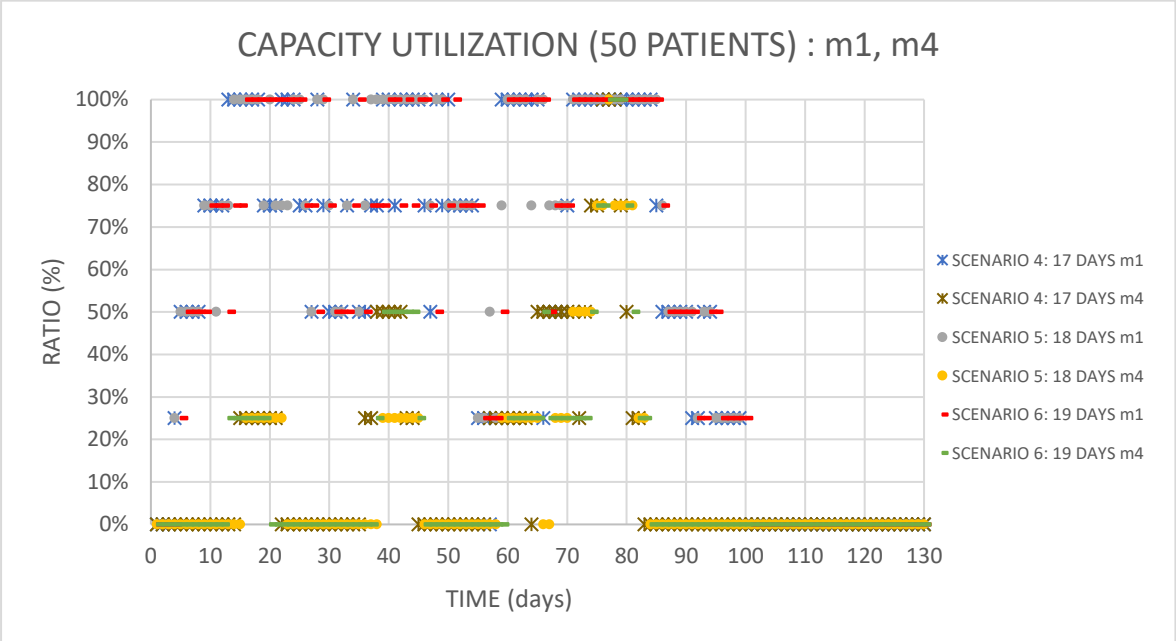

Figure 8: Capacity utilization of m1 and m4 for 50 patients

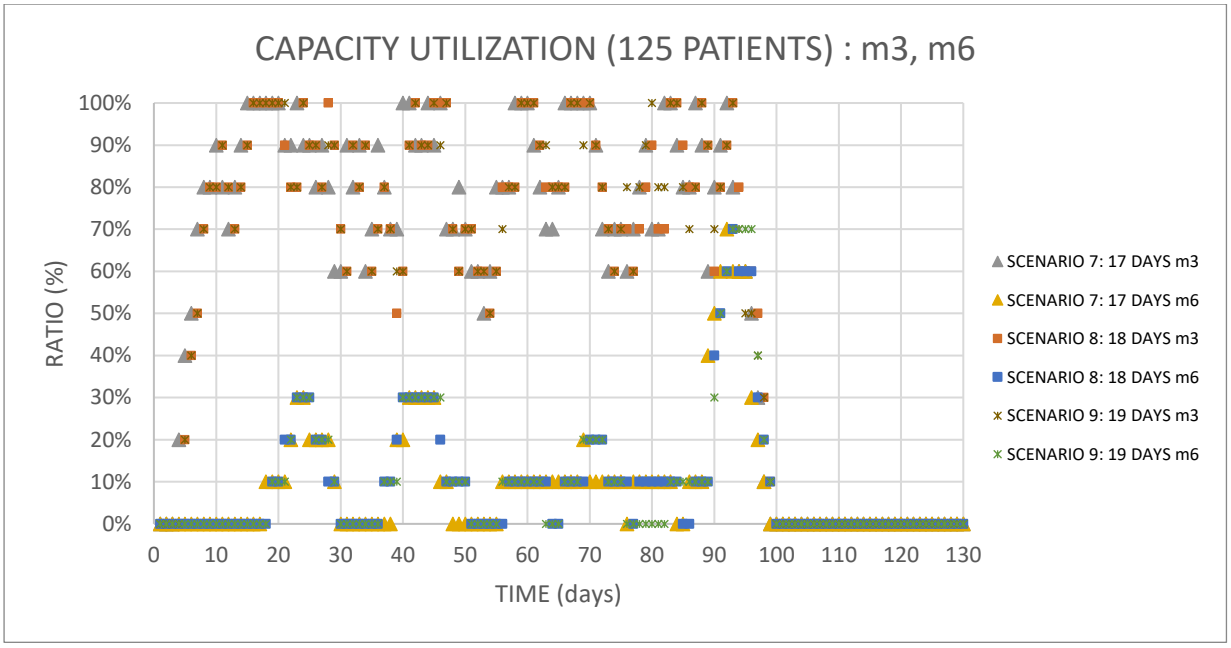

Figure 9: Capacity utilization of m3 and m6 for 125 patients

It is observed that all the three proposed networks are not fully utilized, although there are chosen by the model as the cost minimizing networks for each scenario. For the demand level of 20 patients, facility m1 is the smallest that can be established but it is still only utilized around 25%. So, another interesting aspect is to consider maximizing the number of patients that an established network can accommodate. This will be presented in paragraph 5.2.

As far as the demand profile of 50 patients is concerned, facility m1 is utilized at around 55% and facility m4 only 10-12% depending on delivery time. The same applies for the 125 patients, where m6 is very little utilized. The fact that the model choses to establish a new facility even though the first one is not fully utilized can be explained by the fact that no delays are considered in this simplified model. This signifies that if a new patient arrives and the manufacturing facility is full, a new one is automatically established. So, it is imperative to investigate what will happen if delays and waiting time is allowed, to minimize the investment costs and as a result the total cost of the therapies. This will be discussed in paragraph 4.2.

CHAPTER 3: RESEARCH CHALLENGES AND THESIS OBJECTIVE

3.1 THE MULTI-OBJECTIVE OPTIMIZATION MODEL

In the model described above there are two conflicting objectives, minimization of cost and minimization of return time of therapies. As a result, it is essential to evaluate the trade-off between the two objectives. On the one hand, cost minimization is very important, since CAR-T cell therapies are very expensive. On the other hand, return time must be minimized too, because these therapies are addressed to terminally ill cancer patients that the sooner, they get their therapy the better. The aim of the new model is to express the possible solutions as a set of pareto optima, representing optimal trade-offs between given criteria. To do that, two methods will be assessed. One is the weighted sum method, where the two objectives are expressed into a single objective function and each of them is multiplied by a weight factor. The second one is the epsilon constraint method, where only one objective is expressed in the objective function, and the other one is constraint under the epsilon value. Results of each method will be compared to identify the most efficient one.

3.2 ROBUSTNESS OF THE SUPPLY CHAIN

In an industry such as the one with the CAR T cell therapies, demand can be unexpected, so it is very important to represent the ability of each of the proposed networks to absorb unexpected demand.

3.2.1 MAXIMUM CAPACITY OF EACH OF THE PROPOSED NETWORKS

First, the three networks proposed by the multi-objective model will be tested under uncertain demand to check the highest demand that they can accommodate. The method to do that is by developing a new model where the network is fixed but the demand profile is not given (like it was before). The user inputs the total demand (e.g. 50 patients) and the model must allocate them in an optimal way to accommodate all or most of them. So, different volumes of demand are tested for each network, until the model becomes infeasible.

3.2.2 NEED TO OVER-DESIGN

When the maximum demand is reached, it is checked which one of the nodes becomes saturated first, meaning that this node blocks the whole network. Saturation as a concept will compare the static model to a dynamic one. It is assumed that there is a leeway of 25% imposed in the current capacity, which will be set free in the following cases. The results will report how such a leeway translate into the networks ability to cope as a whole. Also, it will be seen which units must be over-designed to absorb shocks in the demand.

3.2.3 ALTERNATIVE NETWORKS

A usual procedure in industry is to rent part of other manufacturers' facilities instead of establishing new ones. It is very useful to evaluate how a network with overall the same capacity split into different manufacturing facilities will respond at different demand levels.

3.2.4 REALISTIC SCENARIO WITH DELAYS

The last round of experiments involves a more realistic approach, where patients may face delays and waiting time before each procedure. In all the above scenaria when a patient entered the leukapheresis site, he/she was immediately served and the procedure for the manufacturing of the therapy started instantly. This means that if a patient arrives and the manufacturing facility is full, a new one is established. This leads to augmentation of the total cost of the therapy. However, in real life, delays are possible and if the patient arrives when there is no room for him/her to be accommodated, he/she will have to get in a waiting list until a spot opens. This step is very important to be depicted in the model since, it will significantly decrease the costs, which is a main goal at this point. Waiting time will be considered after the patient enter the leukapheresis site and before the leukapheresis procedure. In that way, shelf-life problems are avoided. However, a maximum time of waiting time will be applied as a constraint, because cancer patients in the last stages cannot afford very long waiting lists.

CHAPTER 4: METHODOLOGY

The modifications made to the original model to accommodate the new research objectives will be analyzed in this chapter. The new variables and equations that were employed, as well as the new objective function for each scenario are presented. First, the methodology for the multi-objective optimization, both the weighted sum and the ε-constraint, is depicted. The necessary changes to allow optimal allocation of patients follow and lastly the nomenclature and equations needed for the more realistic model with delays are displayed.

4.1 MULTI-OBJECTIVE MODEL

4.1.1 WEIGHTED SUM METHOD

There were some necessary changes that were made in the above model to allow the multi-objective optimization, using the weighted sum method.

First of all, the objective function changes so that apart from the total cost it will also include the return time. Time is no longer a constrained variable.

The new objective function:

- $\text{OBJECTIVE}=\min(a*\sum_p \text{NORMTC}_p+(1-a)*\sum_p \text{NORMTRT}_p)$ (A.38)

It should be mentioned that cost and return time are on different numerical scales, cost is in millions, whereas time is only in days 17-19. As a result, they should be normalized before being used in a single objective function. Otherwise, cost will always prevail the impact of time on the objective.

- $\text{NORMTC}_p = \frac{TCPT_p - \min(TCPT_p)}{\max(TCPT_p) - \min(TCPT_p)}$, where min and max TCPT_p (total cost per therapy) are calculated for each scenario using the single objective model. (A.39)
- $\text{NORMRT}_p = \frac{TRT_p - \min(TRT_p)}{\max(TRT_p) - \min(TRT_p)}$, where min and max TRT_p (total return time per therapy) are calculated for each scenario using the single objective model. (A.40)

Moreover, the time constraint is deleted from the model, as time is now an objective.

- ~~$TRT_p \leq 18$~~

4.1.2 EPSILON CONSTRAINT METHOD

In this case the objective function that it is used is the same as the single objective model.

$$min\ TOTCOST = \sum p\ CTMp + \sum p\ TTCp + \sum p\ CQCp$$

However, there is a new time constraint:

- $ATRT \leq$ epsilon, where epsilon is from 17 to 19 changing by 0.1.

4.2 DEMAND MAXIMIZATION AND ROBUSTNESS OF SUPPLY CHAIN

4.2.1 OPTIMAL ALLOCATION OF PATIENTS

In this version, the network is fixed and the goal is to maximize the number of patients that it can accommodate.

The new variables that are added:

Nomenclature	
Indices	
CAPC	*Capacity of leukapheresis site*
$CAPL_{c,t}$	*capacity of leukapheresis site c at time t*

First of all, since the manufacturing facilities and the links between nodes are established, the binary variables E1, X1 and X3 are eliminated from the model and inputs for them are given as parameters. Along with them, the following constraints are deleted:

- ~~$X1_{c,m} \leq E1_m, \forall c, m$~~
- ~~$X2_{m,h} \leq E1_m, \forall c, m$~~

Moreover, the time constraint is also removed as to allow the maximum number of patients that can be accommodated.

- ~~$TRT_p \leq 18$~~

Also, a new objective function is employed:

- $\text{OBJECTIVE}=\text{Np}-\sum_{p,\text{h,t}} \text{INH}_{\text{p,h,t}}$ (A.41)

The aim is to minimize the difference between incoming patients and treated patients, which practically means maximize the number of served patients. It should be mentioned here that INH (number of patients that get the therapy) is used in the objective function and not INC (number of patients that come to the leukapheresis site). This helps to ensure that there are not patients that enter the leukapheresis site but cannot be accommodated in time by the manufacturing facility.

Also, new equations are inserted to control the new challenges associated with the unknown demand profile.

Equation (A.42) ensures that each patient is entered in only one leukapheresis site and only once.

- $\sum_{\text{c,t}} \text{INC}_{\text{p,c,t}} = 1$ (A.42)

Equation (A.43) ensures that no more than 8 patients are entered each day in total.

- $\sum_{\text{p}} \text{INC}_{\text{p,c,t}} \leq 8$ (A.43)

Equation (A.44) gives the capacity of each leukapheresis site c at every time t, whilst Equation (A.45) makes sure that the therapies do not exceed the available capacity of each leukapheresis site site.

- $CAP_{\text{c},t} = FCA\text{C} - \sum_p INC_{p,\text{c},t}$, $\forall p$, c,t (A.44)
- $\sum_p INC_{p,\text{c},t} - \sum_p OUTC_{p,\text{c},,t} \leq CAP\text{L}_{\text{c},t}$, $\forall p$, c,t (A.45)

4.2.2 WAITING TIME

In this set of scenarios, it is known from 4.2.1 the maximum number of patients that each network can accommodate if we allow optimal allocation in leukapheresis sites. However, this is something very difficult to happen in real life as these therapies are addressed to terminally ill cancer patients that will not be able to travel. So, having this in mind, given demand profiles (the same that were used in the single objective model) are used and it is evaluated how the cost and return time for each therapy will change if waiting time is allowed.

The new variables that are employed:

Nomenclature	
Indices	
d	*Possible waiting time*
$twait_d$	*Days waiting in the leukapheresis site*
Maxwait	*Maximum waiting time*
$W_{p,c,d,t}$	*1 if patient waits*
$INW_{p,c,d,t}$	*Therapy p getting in waiting list at leukapheresis site c at time t*
$OUTW_{p,c,d,t}$	*Therapy p getting out of waiting list at leukapheresis site c at time*
$INC2_{p,c,t}$	*Patient getting out of waiting and getting in for the leukapheresis*

Again, in this model, the time constraint is removed.

- ~~$TRT_p \leq 18$~~

The objective function is the following the goal is to minimize the total cost by increasing delivery time.

- $min\ TOTCOST = \sum p\ CTMp + \sum p\ TTCp + \sum p\ CQCp + \sum p\ C\mathrm{WAIT}p$

Equation (A.46) calculates the total cost for each patient.

- $C\mathrm{WAIT}_p = \sum_{c,d,t} \mathrm{W1}_{p,c,d,t} * \mathrm{twait}_d * 100\ ,\ \forall\ p$ (A.46)

Equation (A.47) ensures that all incoming patients are considered for waiting time

- $\mathrm{INC}_{p,c,t} = \sum_{d} INW_{p,c,d,t}, \forall p, c, t$ (A.47)

Equation (A.48) ensures that all patients in the waiting list eventually come out and (A.49) ensures that everyone that comes out of the waiting list get into the leukapheresis procedure.

- $INW_{p,c,d,t} = \mathrm{OUTW}_{p,c,d,t+\mathrm{twait}}$ (A.48)
- $\mathrm{INC2}_{p,c,t} = \sum_{d} \mathrm{OUTW}_{p,c,d,t}$ (A.48)

Equation (A.49) ensures that all patients get out of the leukapheresis site after the leukapheresis procedure.

- $\mathrm{INC2}_{p,c,t} = \mathrm{OUTC}_{p,c,,t+1}$ (A.49)

Equations (A.50)-(A.51) confirm that a minimum and maximum flow of material exists for a transportation link to be established.

- $INW_{p,c,d,t} \geq \mathrm{W1}_{p,c,d,t} * \mathrm{FMIN}$ (A.50)
- $INW_{p,c,d,t} \leq \mathrm{W1}_{p,c,d,t} * \mathrm{FMAX}$ (A.51)

Equation (A.52) ensures that each patient is only assigned once in the waiting list.

- $\sum_{c,d,t} \mathrm{W1}_{p,c,d,t} = 1$ (A.52)

4.3 IMPLEMENTATION

All the models have been implemented in GAMS Release 24.8.5 r61358 WEX-WEI x86 64bit/MS Windows and solved with CPLEX 12.9.0. All computational experiments were performed in a core i-5 Toshiba SATELLITE PROA50-EC-139 machine with 8GB of RAM running the 64bit/MS Windows. The data for all the cases examined in this thesis, as well as the GAMS code, can be made available upon request.

CHAPTER 5: RESULTS AND DISCUSSION

5.1 MULTI-OBJECTIVE OPTIMIZATION

5.1.1 WEIGHTED SUM METHOD

The first multi-objective optimization method to be evaluated is the weighted sum method, where, as explained in paragraphs 1 and 3, the two objectives are expressed into a single objective function, each multiplied by a weight factor.

- OBJECTIVE=min(a*$\sum_p$NORMTC$_p$+(1-a) *$\sum_p$NORMTRT$_p$) (A.38)
- NORMTC$_p$ $=\frac{TCPT_p-\min(TCPT_p)}{\max(TCPT_p)-\min(TCPT_p)}$, where min and max TCPT$_p$ (total cost per therapy) are calculated for each scenario using the single objective model. (A.39)
- NORMRT$_p$ $=\frac{TRT_p-\min(TRT_p)}{\max(TRT_p)-\min(TRT_p)}$, where min and max TRT$_p$ (total return time per therapy) are calculated for each scenario using the single objective model. (A.40)

The alpha factor is progressively increased from 0 to 1 by a step of 0,05. When the alpha equals 0 it means that the cost is not considered in the minimization process, while when alpha equals 1, time is not considered as an objective.

For the different values of alpha the following results are obtained:

5.1.1.1 20 PATIENTS

Table 7: Weighted sum method for 20 patients

NUMBER OF PATIENTS: 20					
Established Facilities	alpha	Total Cost (M $)	Cost per Therapy (K $)	Average Return Time (days)	Optimality gap
m1, m5	0	26,063	1303.2	17.00	0%
m1	0.05	3,48	174.0	17	0%
	0.1	3,48	174.0	17	0%
	0.15	3,48	174.0	17	0%
	0.2	3,48	174.0	17	0%
	0.25	3,48	174.0	17	0%
	0.3	3,48	174.0	17	0%
	0.35	3,48	174.0	17	0%
	0.4	3,48	174.0	17	0%
	0.45	3,46	173.1	17.45	0%
	0.5	3,46	173.1	17.45	0%
	0.55	3,45	172.7	17.75	0%
	0.6	3,44	172.5	18	0%
	0.65	3,43	171.8	18.70	0%
	0.7	3,43	171.8	18.70	0%
	0.75	3,43	171.8	18.70	0%
	0.8	3,43	171.6	19	0%
	0.85	3,43	171.6	19	0%
	0.9	3,43	171.6	19	0%
	1	3,43	171.6	19	0%

Table 8: Single objective model for 20 patients[18]

SINGLE OBJECTIVE MODEL		
Average Return Time (days)	Total Cost (M $)	Cost per Therapy (K $)
17	3,48	174,1
18	3,45	172,6
19	3,43	171,6

Comparing the results from the single objective model and the multi-objective, it is stated that the multi objective model reproduces and verifies the results of the single objective model. As far as the return times of 17 and 19 days the total cost by the two models is the same. However, at the 18 days the multi-objective model calculates a slightly lower total cost. This can be explained by the fact that this model uses the average return time as the optimizing objective. So, some patients might have return times of 19 days, some of 17 days and some of 18 days but the average equals 18. In contrast, in the single objective model all patients have a return time of 18 days, because this is given as a constraint by the user.

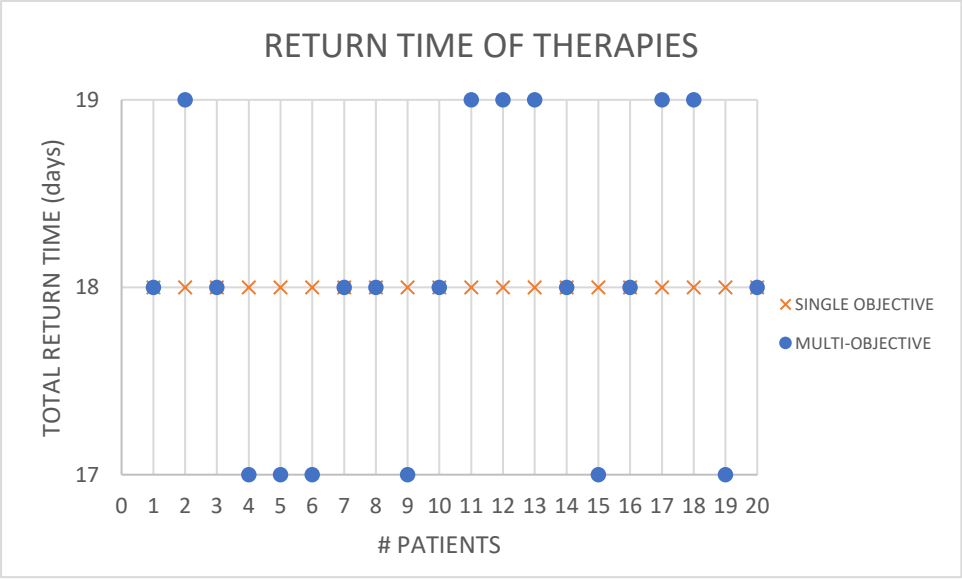

Figure 10: return time of therapies – 20 patients

Another point worth mentioning is the results when alpha equals 0. At this point cost is omitted from the objective function and as a result the algorithm stops when it finds the first solution minimizing delivery time. Thus, the depicted cost is not realistic and should not be taken under consideration.

As it has been mentioned before, the prices present an uncertainty at around 20%, because the market of CAR-T cell therapies is very new and there are not enough data available.

The pareto curve that depicts the above results is the following:

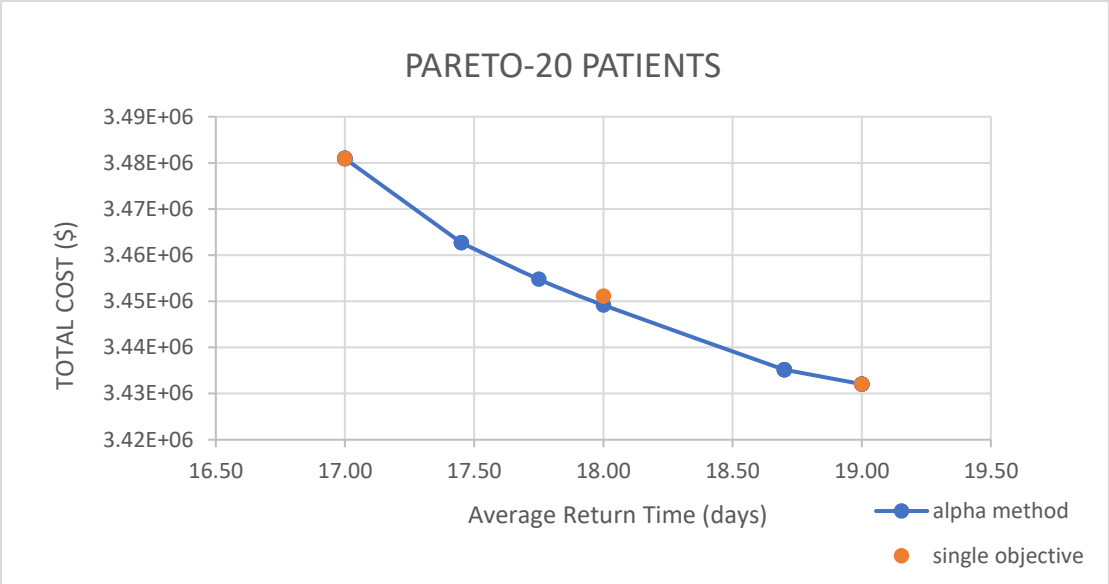

Figure 11: Pareto curve for 20 patients with the weighted sum method

5.1.1.2 50 PATIENTS

The same analysis is done for the demand profile of 50 patients.

Table 9: Weighted sum method for 50 patients

NUMBER OF PATIENTS: 50					
Established Facilities	alpha	Total Cost (M $)	Cost per Therapy (K $)	Average Return Time (days)	Optimality gap
m1, m2	0	26.73	534.5	17	0%
m1, m4	0.05	7.22	144.4	17	0%
	0.1	7.22	144.4	17	0%
	0.15	7.22	144.4	17	0%
	0.2	7.22	144.4	17	0%
	0.25	7.22	144.4	17	0%
	0.3	7.22	144.4	17	0%
	0.35	7.22	144.4	17	0%
	0.4	7.22	144.4	17	0%
	0.45	7.21	144.2	17.06	0%
	0.5	7.21	144.2	17.06	0%
	0.55	7.16	143.2	17.58	0%
	0.6	7.16	143.2	17.58	0%
	0.65	7.14	142.9	17.8	0%
	0.7	7.10	141.9	18.7	0%
	0.75	7.09	141.9	18.76	0%
	0.8	7.09	141.9	18.8	0%
	0.85	7.09	141.8	18.98	0%
	0.9	7.09	141.8	18.98	0%
	1	7.09	141.8	18.98	0%

Table 10: Single objective model for 50 patients [18]

SINGLE OBJECTIVE MODEL		
Average Return Time (days)	Total Cost (M $)	Cost per Therapy (K $)
17	7,22	144,4
18	7,14	142,7
19	7,09	141,8

And the pareto curve:

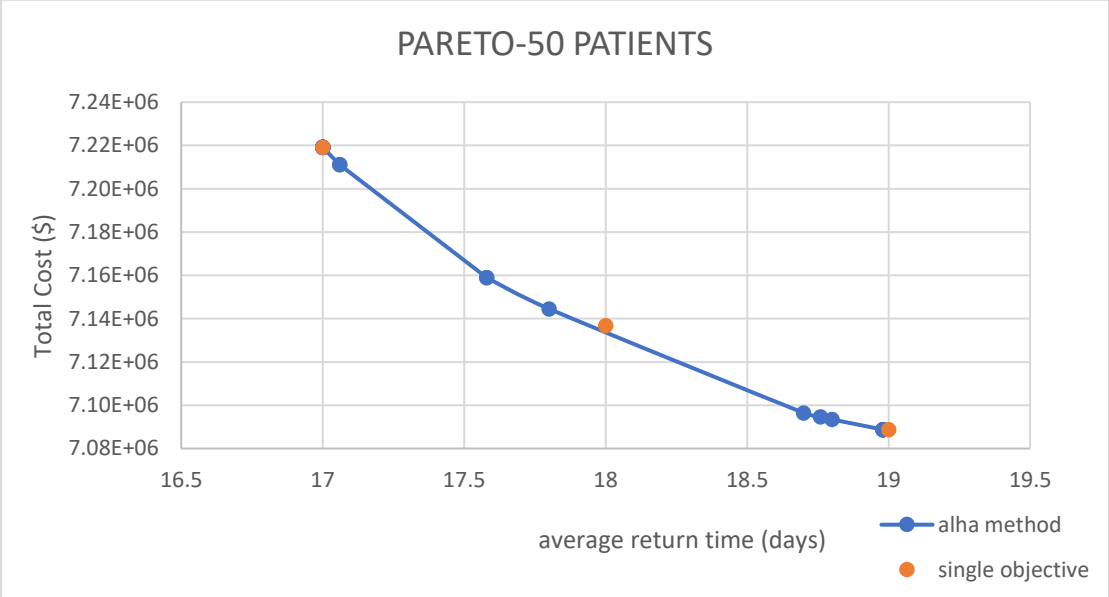

Figure 12: Pareto curve for 50 patients with the weighted sum method

5.1.1.3 125 PATIENTS

The results for 125 patients follow:

Table 11: Weighted sum method for 125 patients

NUMBER OF PATIENTS: 125					
Established Facilities	alpha	Total Cost (M $)	Cost per Therapy (K $)	Average Return Time (days)	Optimality gap
m2, m6	0	33.14	265.1	17	0%
m3, m6	0.05	18.23	145.8	17	0%
	0.1	18.23	145.8	17	0%
	0.15	18.23	145.8	17	0%
	0.2	18.23	145.8	17	0%
	0.25	18.23	145.8	17	0%
	0.3	18.23	145.8	17	0%
	0.35	18.23	145.8	17	0%
	0.4	18.23	145.8	17	0%
	0.45	18.22	145.7	17	0%
	0.5	18.07	144.6	17.568	0%
	0.55	17.97	143.8	17.992	0%
	0.6	17.97	143.7	18	0%
	0.65	17.84	142.8	18.856	0%
	0.7	17.83	142.6	19	0%
	0.75	17.83	142.6	19	0%
	0.8	17.83	142.6	19	0%
	0.85	17.83	142.6	19	0%
	0.9	17.83	142.6	19	0%
	1	17.83	142.6	19	0%

Table 12: Single objective model for 125 patients [18]

SINGLE OBJECTIVE MODEL		
Average Return Time (days)	Total Cost (M $)	Cost per Therapy (K $)
17	18,23	145,8
18	17,97	143,7
19	17,83	142,6

The pareto curve for 125 patients:

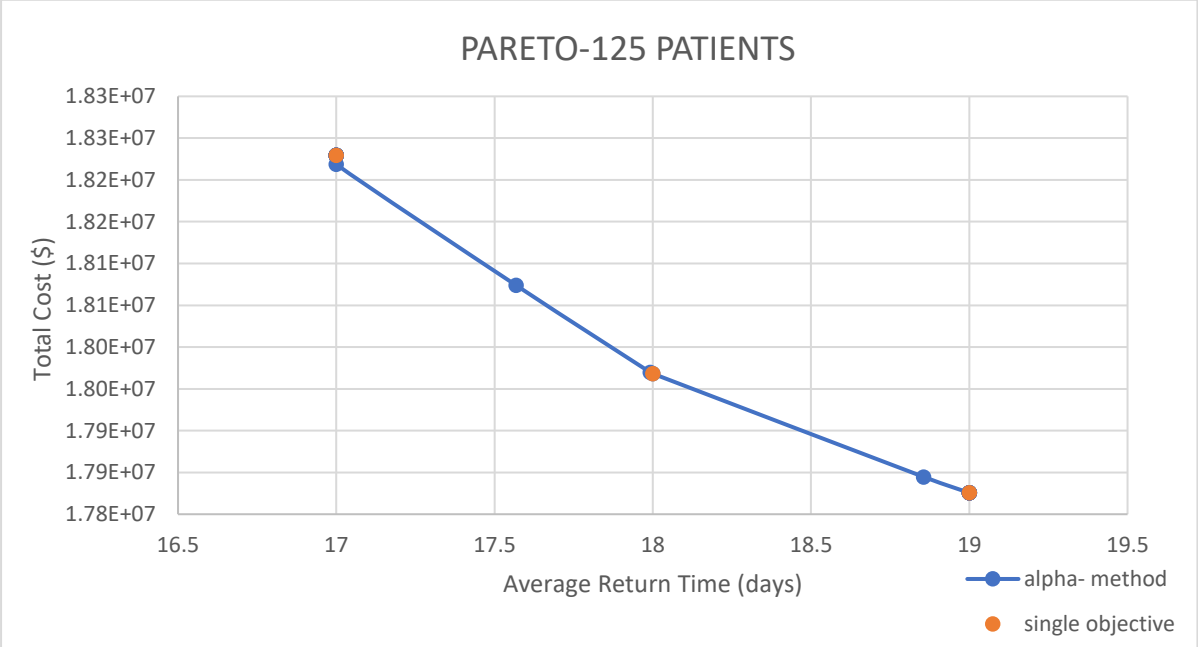

Figure 13: Pareto curve for 125 patients with the weighted sum method

The same comments, as the demand profile of 20 patients, apply for the profiles of 50 and 125 patients. To conclude, the weighted sum method produces reasonable results similar to the single objective model. However, even though the alpha is discretized a lot, the model produces result at a very few time points. For this reason, it is necessary to evaluate another method, the epsilon constraint to see if more pareto points can be obtained.

5.1.2 Epsilon Constraint method

In this case the objective function that it is used is the same as the single objective model and the return time is constraint under the epsilon value:

- $min\ TOTCOST = \sum_p CTM_p + \sum_p TTC_p + \sum_p CQC_p$
- $ATRT \leq$ epsilon, where epsilon is from 17 to 19 changing by 0.1.

5.1.2.1 20 PATIENTS

Table 13: Epsilon-constraint method for 20 patients

NUMBER OF PATIENTS: 20					
Established Facilities	epsilon	Total Cost (M $)	Cost per Therapy (K $)	Average Return Time (days)	Optimality gap
m1	17	3.48	174.0	17	0%
	17.1	3.48	173.8	17.1	0%
	17.2	3.47	173.6	17.2	0%
	17.3	3.47	173.4	17.3	0%
	17.4	3.46	173.2	17.4	0%
	17.5	3.46	173.1	17.5	0%
	17.6	3.46	172.9	17.6	0%
	17.7	3.46	172.8	17.7	0%
	17.8	3.45	172.7	17.8	0%
	17.9	3.45	172.6	17.9	0%
	18	3.45	172.5	18	0%
	18.1	3.45	172.4	18.1	0%
	18.2	3.45	172.3	18.2	0%
	18.3	3.44	172.2	18.3	0%
	18.4	3.44	172.1	18.4	0%
	18.5	3.44	172.0	18.5	0%
	18.6	3.44	171.9	18.6	0%
	18.7	3.44	171.8	18.7	0%
	18.8	3.43	171.7	18.8	0%
	18.9	3.43	171.7	18.9	0%
	19	3.43	171.6	19	0%

Table 11: Single objective model for 20 patients[18]

SINGLE OBJECTIVE MODEL		
Average Return Time (days)	Total Cost (M $)	Cost per Therapy (K $)
17	3,48	174,1
18	3,45	172,6
19	3,43	171,6

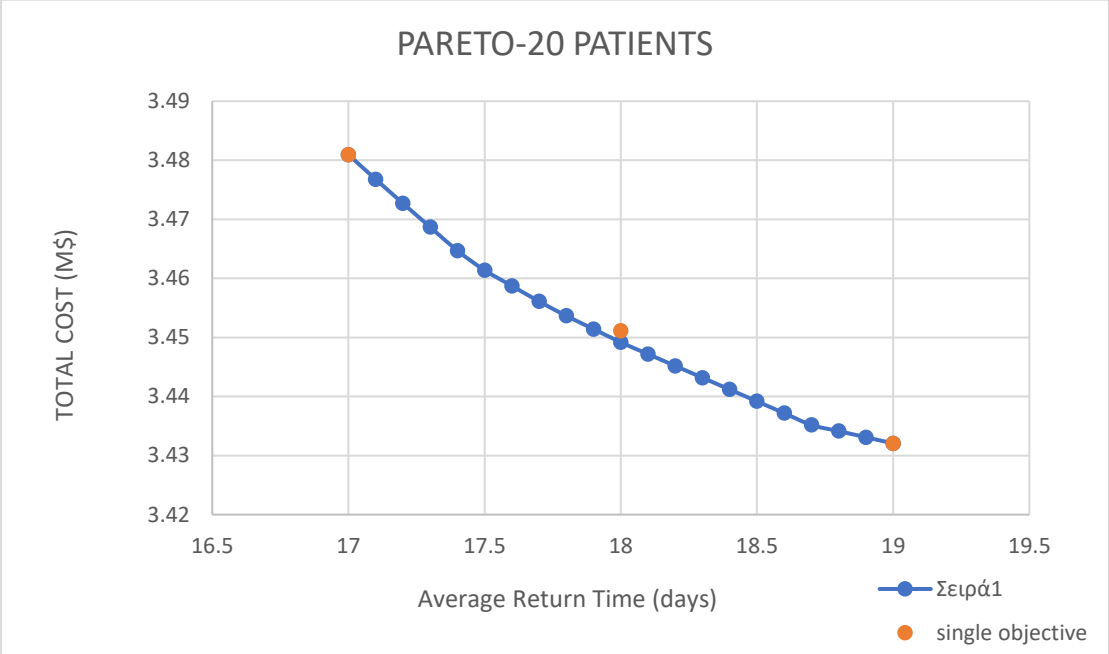

Figure 14: Pareto curve for 20 patients with the epsilon-constraint method

In this case the cost is equal between the single objective model and the multi-objective model for return times 0f 17 and 19 days. However, for the 18 days there is a slight difference between them because in the multi objective model the return time of each therapy is different, and the average is calculated at 18 days.

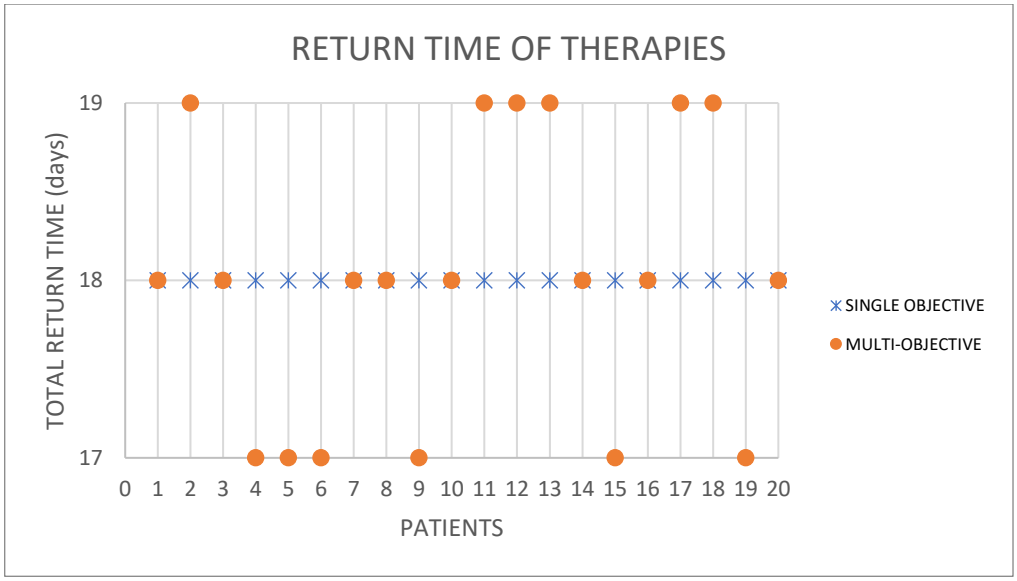

Figure 15: return time of therapies – 20 patients

It should be mentioned that the distribution of patients to different return times in the same as the solution from the weighted sum method. This is expected since both solutions are globally optimal.

5.1.2.2 50 PATIENTS

Table 15: Epsilon-constraint method for 50 patients

NUMBER OF PATIENTS: 50					
Established Facilities	epsilon	Total Cost (M $)	Cost per Therapy (K $)	Average Return Time (days)	Optimality gap
m1, m4	17	7.22	144.4	17	0%
	17.1	7.21	144.1	17.1	0%
	17.2	7.20	143.9	17.2	0%
	17.3	7.19	143.7	17.3	0%
	17.4	7.18	143.5	17.4	0%
	17.5	7.17	143.3	17.5	0%
	17.6	7.16	143.2	17.6	0%
	17.7	7.15	143.0	17.7	0%
	17.8	7.14	142.9	17.8	0%
	17.9	7.14	142.8	17.9	0%
	18	7.13	142.7	18	0%
	18.1	7.13	142.5	18.1	0%
	18.2	7.12	142.4	18.2	0%
	18.3	7.12	142.3	18.3	0%
	18.4	7.11	142.2	18.4	0%
	18.5	7.11	142.1	18.5	0%
	18.6	7.10	142.0	18.6	0%
	18.7	7.10	141.9	18.7	0%
	18.8	7.09	141.9	18.8	0%
	18.9	7.09	141.8	18.9	0%
	19	7.09	141.8	19	0%

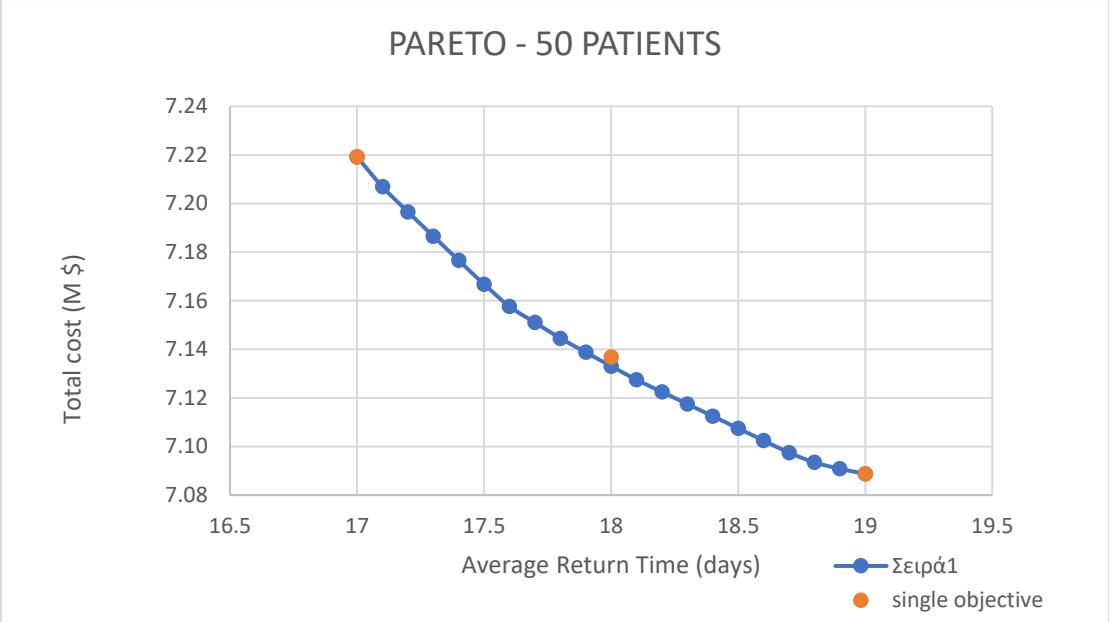

Figure 16: Pareto curve for 50 patients with the epsilon-constraint method

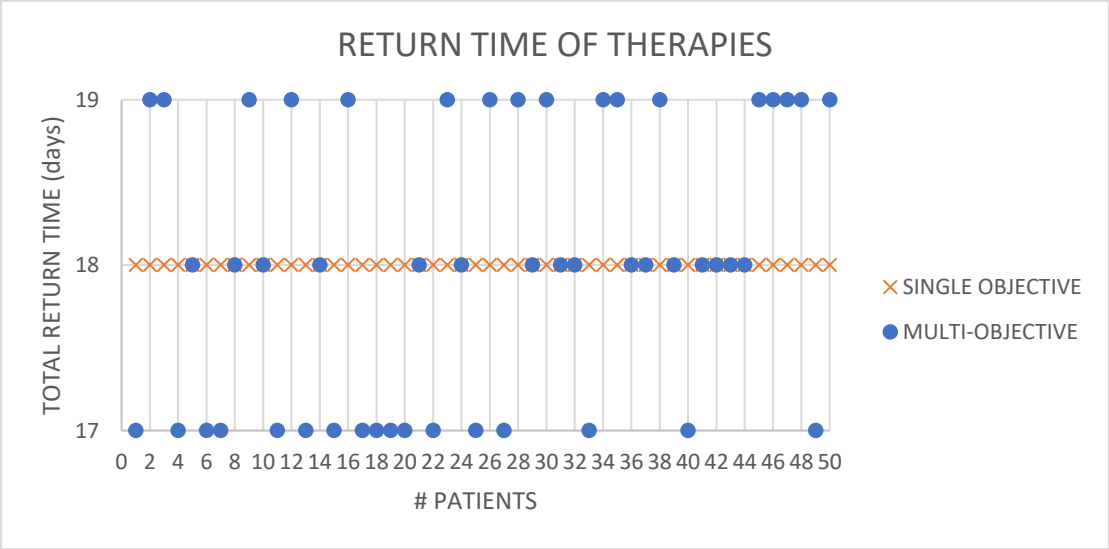

Figure 17: return time of therapies – 50 patients

5.1.2.3 125 PATIENTS

Table 16: Epsilon-constraint method for 125 patients

NUMBER OF PATIENTS: 125					
Established Facilities	epsilon	Total Cost (M $)	Cost per Therapy (K $)	Average Return Time (days)	Optimality gap
m3, m6	17	18.23	145.8	17	0%
	17.1	18.20	145.6	17.1	0%
	17.2	18.17	145.4	17.2	0%
	17.3	18.14	145.2	17.3	0%
	17.4	18.12	144.9	17.4	0%
	17.5	18.09	144.7	17.5	0%
	17.6	18.07	144.5	17.6	0%
	17.7	18.04	144.3	17.7	0%
	17.8	18.02	144.1	17.8	0%
	17.9	17.99	143.9	17.9	0%
	18	17.97	143.7	18	0%
	18.1	17.95	143.6	18.1	0%
	18.2	17.94	143.5	18.2	0%
	18.3	17.93	143.4	18.3	0%
	18.4	17.91	143.3	18.4	0%
	18.5	17.90	143.2	18.5	0%
	18.6	17.88	143.1	18.6	0%
	18.7	17.87	142.9	18.7	0%
	18.8	17.85	142.8	18.8	0%
	18.9	17.84	142.7	18.9	0%
	19	17.83	142.6	19	0%

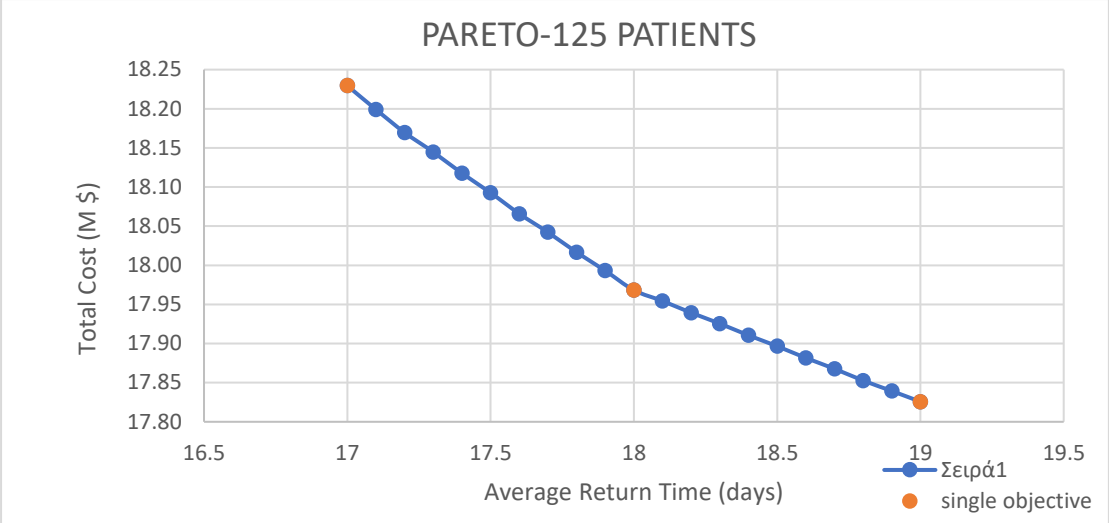

Figure 18: Pareto curve for 125 patients with the epsilon-constraint method

For all three different turnaround times (17, 18 and 19 days) the calculated cost is the same across the two models. In this scenario the optimal solution for an average of 18 days is when all patients get their therapies at 18 days.

5.1.3 COMPARISON

In the weighted sum method, the solution distribution is not uniform, whereas in the epsilon constraint method many more pareto optimal points can be obtained by changing the epsilon value. This problem is intrinsic to the weighted sum method, as it tends to find optimal solutions gathered around certain points. Other disadvantages of the method include: (1) uniformly distributed set of weights does not guarantee a uniformly distributed set of Pareto-optimal solutions, (2) Two different set of weights not necessarily lead to two different Pareto-optimal solutions. Both methods are easy to apply and produce results comparable to each other and to the single objective model.

5.2 DEMAND MAXIMIZATION

In paragraph 3.2 it was discovered that the proposed networks for each demand profile are not fully utilized, although they are the optimal solution for each scenario. This finding leads to consider alternative ways to maximize the utilization of the network and thus reduce the cost per therapy. One way to do this is by allowing optimal allocation of patients in the different leukapheresis sites, which will be dictated by the capacity of the manufacturing facility at each time point. So, instead of having determined demand profiles, the model will be responsible for allocating a given number of patients in the optimal way. The time constraint will also be omitted.

5.2.1 SMALLEST NETWORK

In the first scenario the smallest network (only one manufacturing facility) was chosen for the demand profile of 20 patients. However, the utilization was only around 27%. To begin with, the network was fixed with only m1 being established and demand was progressively increased from 20 to 70 patients, where the model became infeasible.

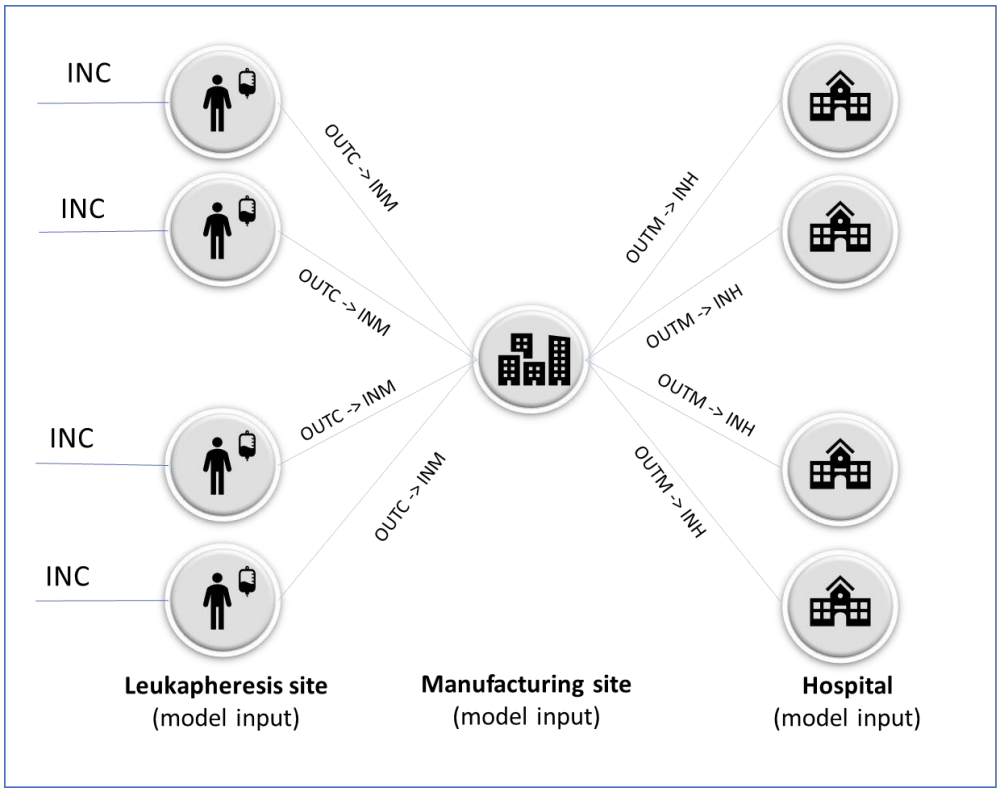

Figure 19: Smallest supply chain network

Network characteristics:

There are 9 nodes in the model.

Nodes in the 1st step are 4 leukapheresis sites. In each unit there is one incoming current (INC) and one that exits (OUTC). Each leukapheresis site is linked with the one established manufacturing facility.

The only node in the 2nd step is 1 manufacturing site. In that, 4 currents get in (INM) and 4 get out (OUTM). The manufacturing facility is linked with 4 leukapheresis sites and 4 hospitals.

Nodes in the 3rd step are 4 hospitals. In each unit there is one incoming current (INH). Each hospital is only linked with the one manufacturing facility.

It is obvious that the node with the most links is the manufacturing facility and as a result it is expected that it will get saturated first.

All the currents are of similar size, there is not much variation in the number of patients that enter or exit each node daily.

The results that were obtained are presented in the following table:

Table 17: Total cost per therapy, average return time and capacity utilization for each demand level – small network

Demand Maximization				
Established Facilities	Number of Patients	Total Cost per Therapy (K $)	Average Return Time	Average utilization (%)
m1 = 4 lines	20	172.7	18.2	30%
	30	122.4	18.3	44%
	40	97.8	17.95	59%
	50	82.6	18.06	74%
	60	72.4	18.1	89%
m1=5 lines	70	65.4	17.94 days	83%

It is noted that the average of the percentage of utilization is calculated for days t4-t122, because t1-t3 leukapheresis and transportation to the manufacturing facility is executed and

t123-t130 quality control and transportation to the leukapheresis site is done. As a result, it is obvious that during this time manufacturing is not possible by default.

In the following diagrams, the percentage of utilization for each day and for each demand level is depicted.

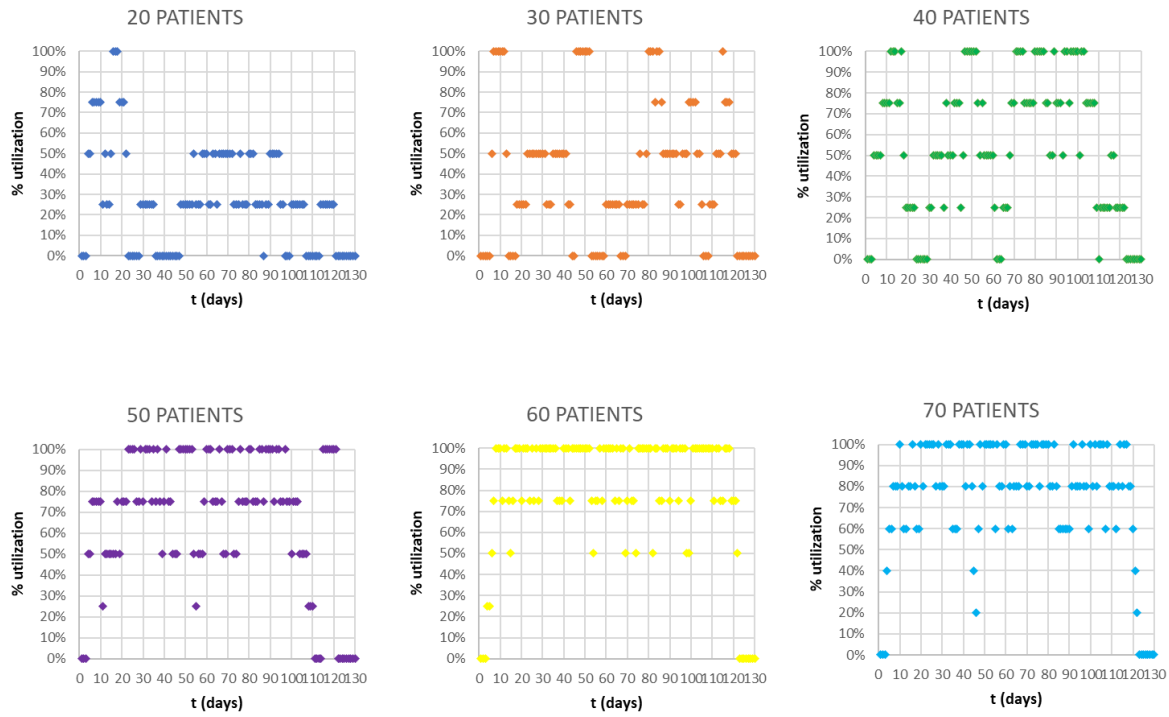

Figure 20: Smallest network – Capacity utilization for different demand levels

Also, there was constructed a diagram showing the relationship between the level of demand, percentage of capacity utilization and the cost per therapy.

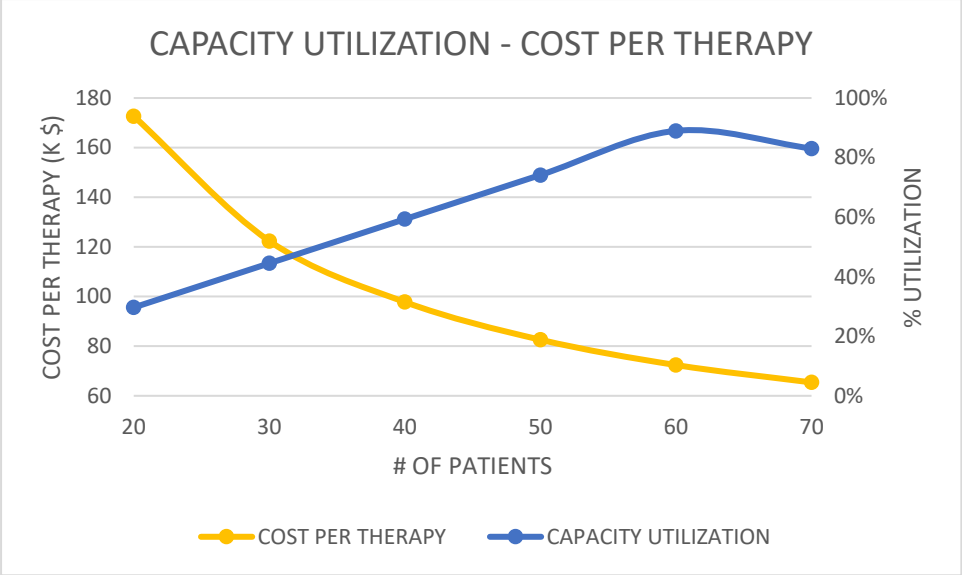

Figure 21: Capacity utilization and cost per therapy in relation to demand level – small network

From all the above, it is concluded that as the number of patient increases, the % of utilization also increases linearly and the cost per therapy decreases.

Subsequently, if the number of patients increased from 20 to 60 utilizing the existing m1 facility, while allowing optimal allocation of patients, the cost per therapy would decrease from 172.7k$ [18] to 72.4k $. This is a very important decrease of 100k$ that must be taken into consideration when designing a product and its supply chain for commercial use.

As far as the robustness of the supply chain and its ability to absorb unexpected shocks in the demand are concerned, it is observed that the first node to get saturated is the second one (manufacturing facility). So, it is suggested that this unit will be over designed to be able to accommodate fluctuations in the demand. We assume there was a 25% leeway in the design, that is set free now and the actual manufacturing facility will have a capacity of 5 lines instead of 4. With this modification then demand that the network can accommodate increases from 60 to 70, a 16,7% increase.

Also, it is observed that average return time of therapies does not have a certain relationship compared to the number of patients, although it was suspected that the higher the demand the higher the return time. For all demand levels, return time is around 18 days with some fluctuations.

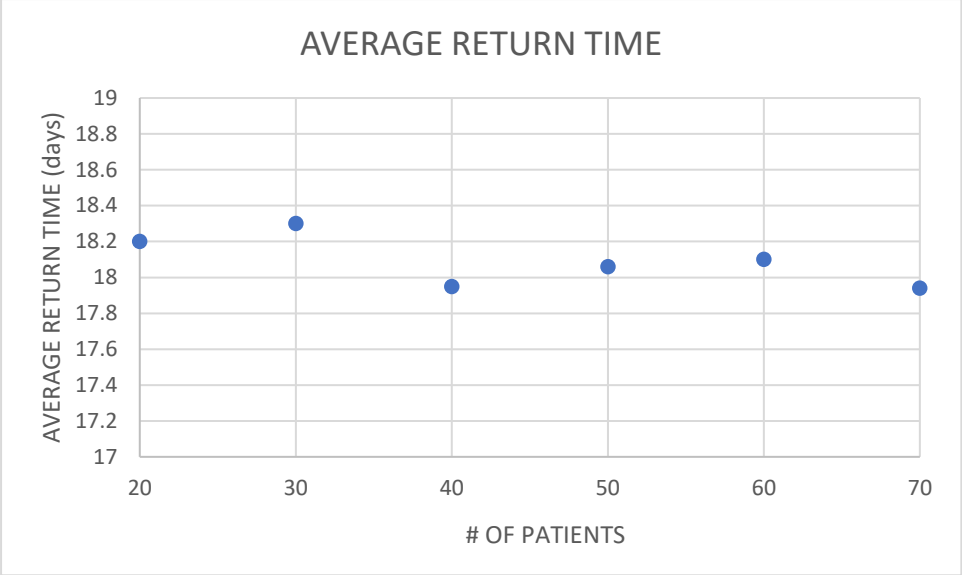

Figure 22: average return time in relation to demand level – small network

5.2.1.1 ALTERNATIVE NETWORKS

In industry it is usual to rent part of existing facilities instead of establishing new ones as it can be more cost effective. It is useful to investigate if a supply chain network with overall the same capacity (4 lines) but more manufacturing facilities being employed can perform equally well.

In this case it is assumed that facilities m1 and m4 are already established and half of each (m1=2 lines, m4=2lines) is rented. It is noted that the cost is not depicted here, since new cost data of renting a facility instead of "building it" are not introduced in the model at this point.

The new network will be:

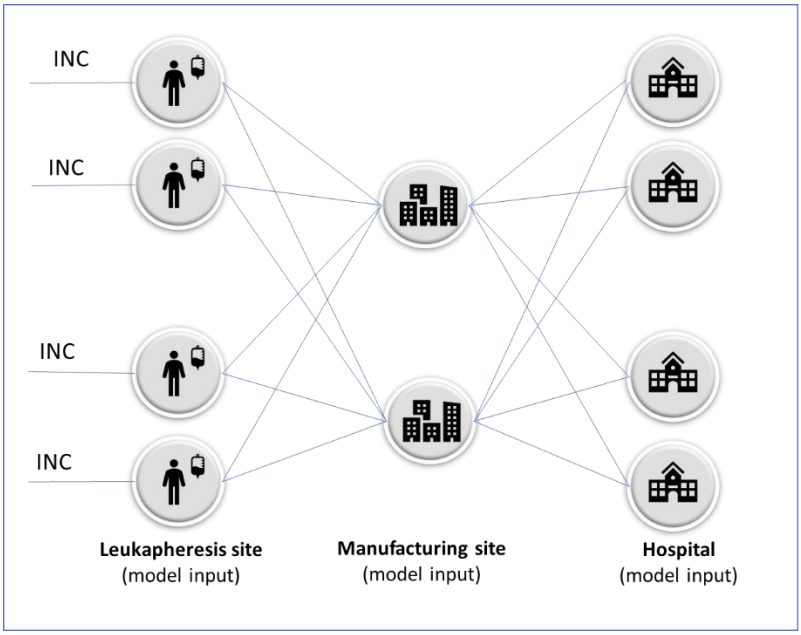

Figure 23: Smallest network – alternative with 2 units

Now each leukapheresis site has two currents that exit, and each hospital has two incoming currents. M1 is located in Stevenage (UK) and m4 in Belgium, while all leukapheresis sites are within the UK, so it is expected that this network has more complex logistics both as return time and transportation costs are concerned.

Table 18: Average return time and capacity utilization for each demand level – alternative small network

Established Facilities	Number of Patients	Average Return Time	Average utilization (%)
m1 = 4 lines	20	18.2	30%
	30	18.3	44%
	40	17.95	59%
	50	18.06	74%
	60	18.1	89%
m1=2 lines m4=2 lines	20	18.2	36%
			24%
	30	18.23	39%
			50%
	40	18	56%
			62%
	50	18.18	71%
			77%
m1=1 line m2=2 lines m3 =1 line	20	18.2	36%
			30%
			24%
	30	17.97	59%
			36%
			47%
	40	18.1	59%
			59%
			59%
	50	18.08	71%
			77%
			71%

For each demand level return time and capacity utilization are similar between the two networks. However, the simple network with one manufacturing facility can accommodate 60 patients while the more complex one can only accommodate 50. This is because by opening more facilities the network becomes more complex, binary variables and constraints increase, thus rendering the model infeasible sooner due to solver running out of memory.

A scenario with three manufacturing facilities is also checked. Specifically, 1 line in manufacturing facility m1, one line in m3 and 2 lines in m2.

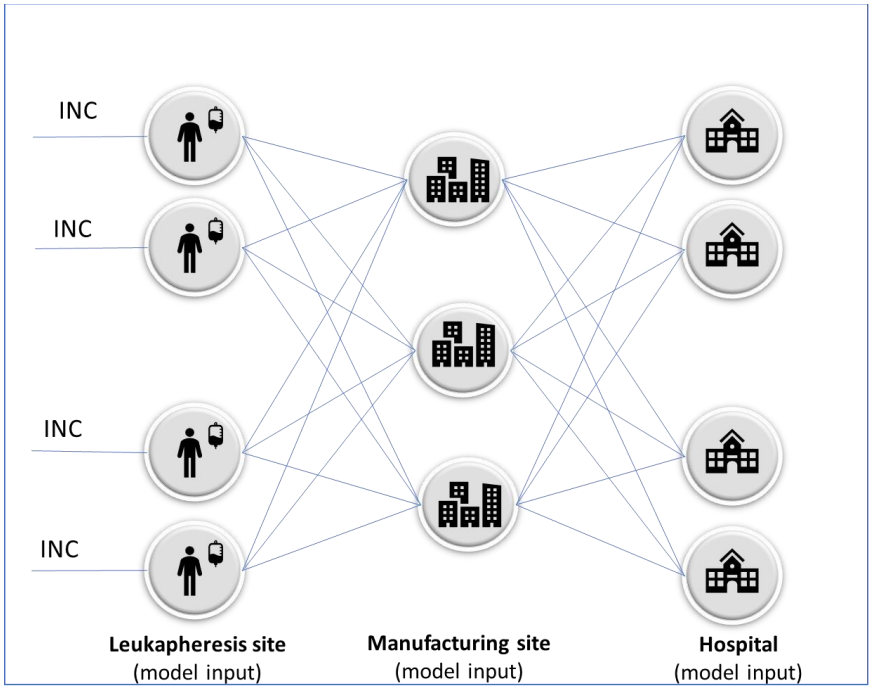

Figure 24: Smallest network – alternative with 3 units

Now each leukapheresis site has three currents that exit, and each hospital has three incoming currents.

The results are similar with the one with 2 manufacturing facilities. Again, the maximum number of patients that can be accommodated are 50 and the average return time 18.08days.

The diagram below depicts the average return time in relation to demand level for the three alternative networks. There is not much variation in the values and all of them are around 18 days.

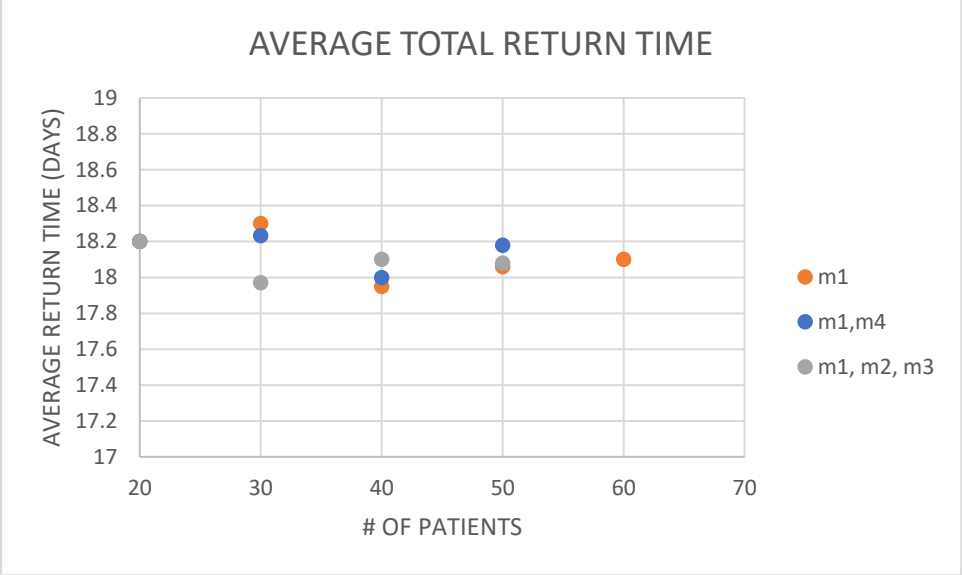

Figure 25: average return time in relation to demand level for the alternative small networks

Since there are no data considering the renting of the facilities, only the transportation cost can be compared between the different networks.

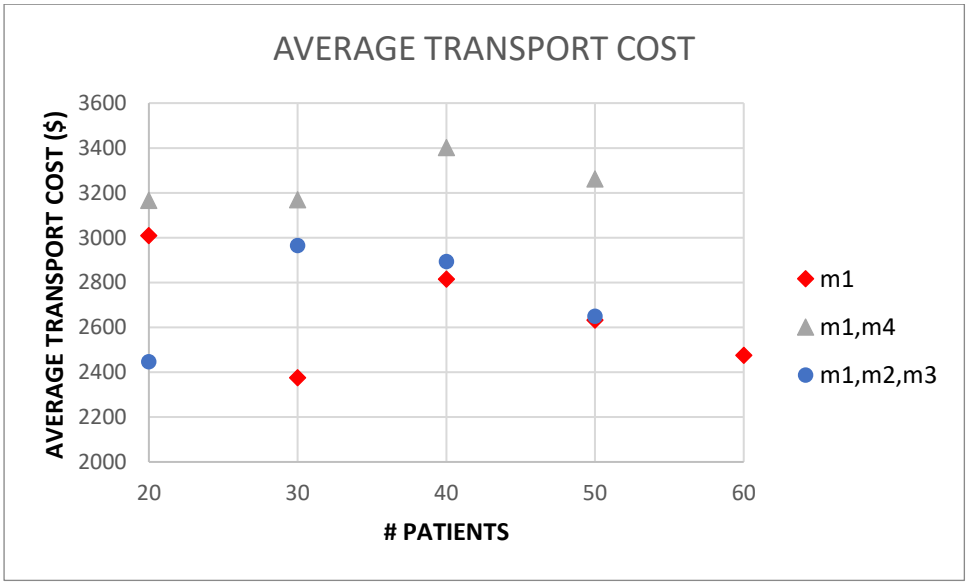

Figure 26: average transport cost in relation to demand level for the alternative small networks

It is observed that the smallest network in almost all demand levels has lower transportation cost. This is reasonable since m1 is located within the uk. Then follows the network with 3 units and the costliest is the network with m1 and m4 because the transportation cost to Belgium is higher.

The above results signify that the alternative networks tested can potentially and theoretically be as efficient as the simpler one. However, because computational difficulty increases with network complexity, the model gives results for demand level of 60 patients only for the simple network. Furthermore, this tactic is usually followed by other businesses, but it is not very suitable for personalized therapies because materials transferred need specific handling and temperature monitoring and the manufacturing facility must be the closest possible to the leukapheresis site and the hospital to eliminate logistic costs and avoid deterioration of the therapies due to multiple transportations.

5.2.2 MEDIUM-SIZED NETWORK

The same steps as in paragraph 4.3.1 will be followed for the bigger network, which includes manufacturing facilities m1 and m4 and was chosen as the optimal for the given demand profile of 50 patients. Again, this network was not fully utilized (m1 around 55%, m4 around 10%). In this paragraph the maximum number of patients that can be accommodated by this network will be evaluated.

Table 19: Total Cost per therapy, average return time and capacity utilization for each demand level – medium-sized network

Demand Maximization				
Established Facilities	Number of Patients	Total Cost per Therapy (K $)	Average Return Time	Average utilization (%)
m1 = 4 lines m4= 4 lines	70	109.2	18.04	46% 58%
	80	98.4	18.03	53% 65%
	90	89.8	18.30	64% 70%
	100	83.4	17.98	77% 71%
m1= 5 lines m4= 5 lines	110	77.9	17.98	71% 59%
	120	73.0	18.18	77% 65%
	130	69.3	18.18	78% 76%

It is noted that the average of the percentage of utilization is calculated for days t4-t122, because t1-t3 leukapheresis and transportation to the manufacturing facility is executed and t123-t130 quality control and transportation to the leukapheresis site is done. As a result, it is obvious that during this time manufacturing is not possible by default.

In the following diagrams, the percentage of utilization of each manufacturing facility for each day and for each demand level is depicted.

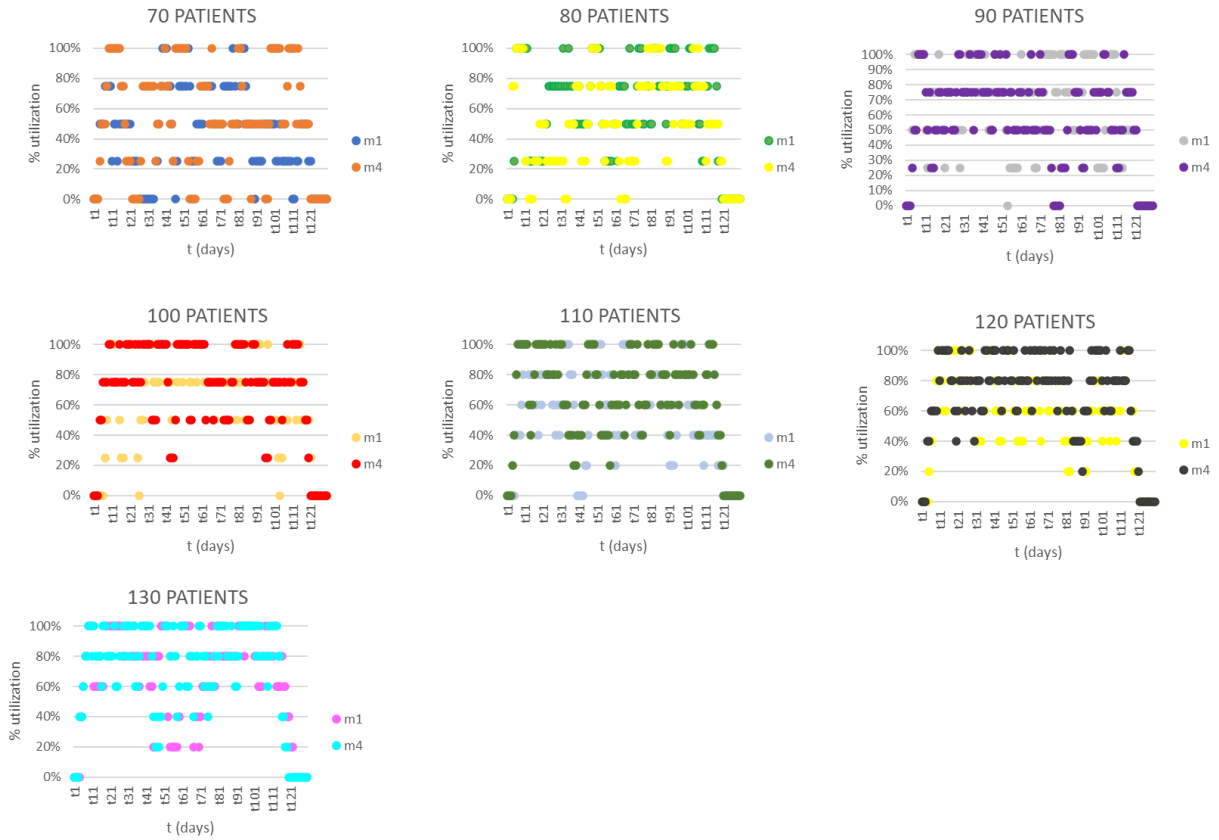

Figure 27: Medium-sized network – Capacity utilization for different demand levels

Also, there was constructed a diagram showing the relationship between the level of demand, percentage of capacity utilization and the cost per therapy.

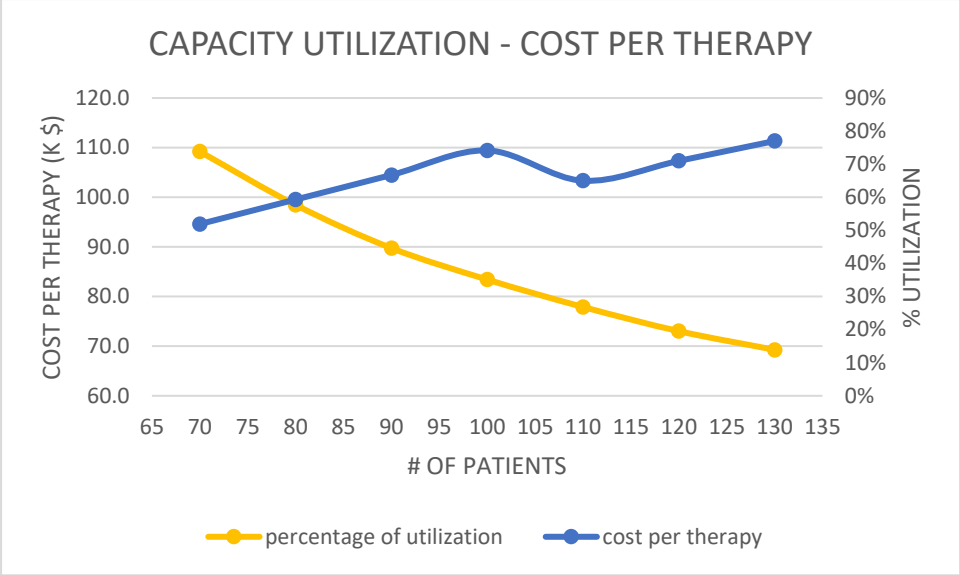

Figure 28: Capacity utilization and cost per therapy in relation to demand level – medium-sized network

From all the above, it is concluded that as the number of patient increases, the % of utilization also increases linearly and the cost per therapy decreases.

Subsequently, if the number of patients increased from 50 to 100 utilizing the existing m1 and m4 facilities, while allowing optimal allocation of patients, the cost per therapy would decrease from 142.7k$ [18]to 83.4k $. This is a very important decrease around 42% that must be taken into consideration when designing a product and its supply chain for commercial use.

It is suggested that the manufacturing facility will be over designed to be able to accommodate fluctuations in the demand. We assume there was a 25% leeway in the design, that is set free now and the actual manufacturing facility will have a capacity of 10 lines instead of 8. With this modification the demand that the network can accommodate increases from 100 to 130, a 30% increase.

Also, it is observed that average return time of therapies does not have a certain relationship compared to the number of patients, although it was suspected that the higher the demand the higher the return time. For all demand levels, return time is around 18 days with some fluctuations.

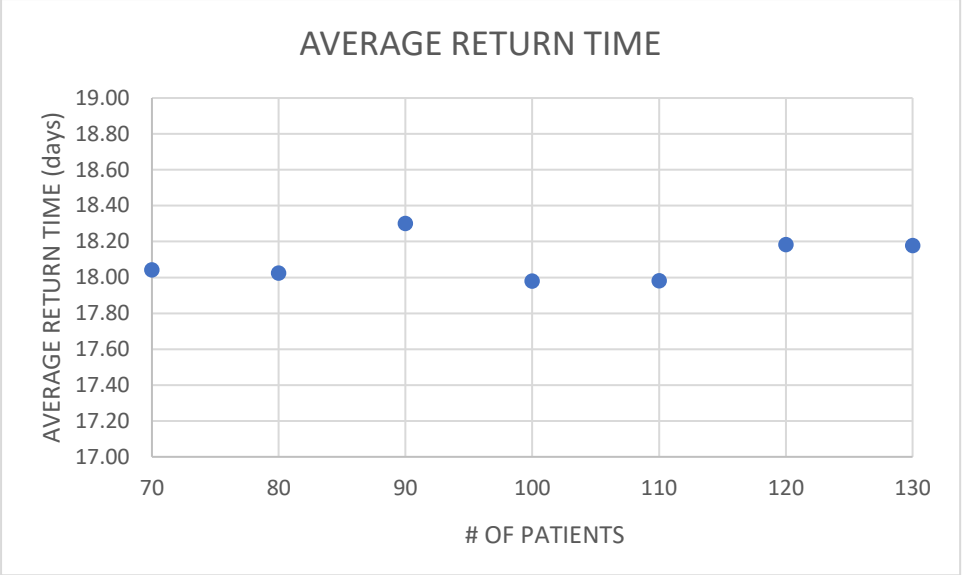

Figure 29: average return time in relation to demand level – medium-sized network

5.2.2.1 ALTERNATIVE NETWORKS

In this case it is assumed that facilities m3 and m4 are already established and part of each (m3=5 lines, m4=3lines) is rented. It is noted that the cost is not depicted here, since new cost data of renting a facility instead of "building it" are not introduced in the model at this point.

Table 20: Average return time and capacity utilization for each demand level – alternative medium-sized network

Established Facilities	Number of Patients	Average Return Time	Average utilization (%)
m1 = 4 lines m4 = 4 lines	70	18.04	46%
			58%
	80	18.03	53%
			65%
	90	17.30	64%
			70%
	100	17.98	77%
			71%
m3=5 lines m4=3 lines	70	18.13	52%
			51%
	80	18.19	59%
			59%
	90	18.08	64%
			71%
	100	18.07	71%
			79%
m3=8 lines	70	18.19	52%
	80	18.21	59%
	90	18.14	67%
	100	17.94	74%
	110	18.07	82%
	120	18.11	89%

For each demand level return time and capacity utilization are similar between the two networks. However, for the simpler network with one manufacturing facility there is a solution up to 120 patients while for the more complex one only up to 100. This is because by opening more facilities the network becomes more complex, binary variables and constraints increase, thus rendering the model infeasible sooner due to solver running out of memory.

A scenario with three manufacturing facilities is also checked. Specifically, 2 lines in manufacturing facility m1, 4 lines in m3 and 2 lines in m4.

The results are similar with the one with 2 manufacturing facilities. Again, the maximum number of patients that can be accommodated are 50 and the average return time 18.08days.

The diagram below depicts the average return time in relation to demand level for the three alternative networks. There is not much variation in the values and all of them are around 18 days.

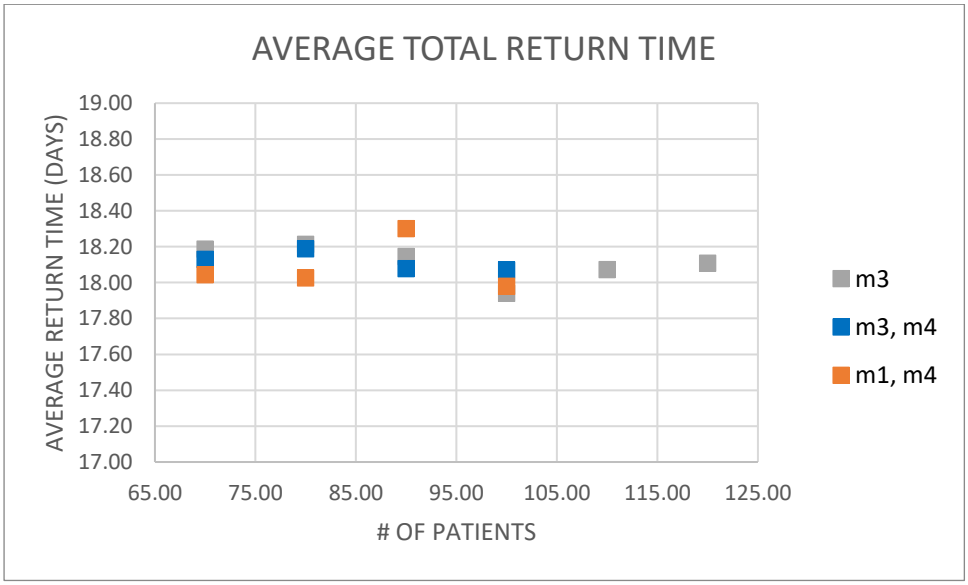

Figure 30: Average return time in relation to demand level for the alternative medium-sized networks

The above results signify that the alternative networks tested can potentially and theoretically be as efficient as the simpler one. However, because computational difficulty increases with network complexity, the model gives results for demand level of 120 patients only for the simple network. But also, this usual tactic followed by other businesses is not very suitable for personalized therapies because materials transferred need very specific handling and temperature monitoring and the manufacturing facility must be the closest possible to the leukapheresis site and the hospital to eliminate logistic costs and avoid deterioration of the

therapies due to multiple transportations. These alternative networks could be short-term solutions for the near future because during this time it is supposed that the "new" manufacturing facilities will be under construction.

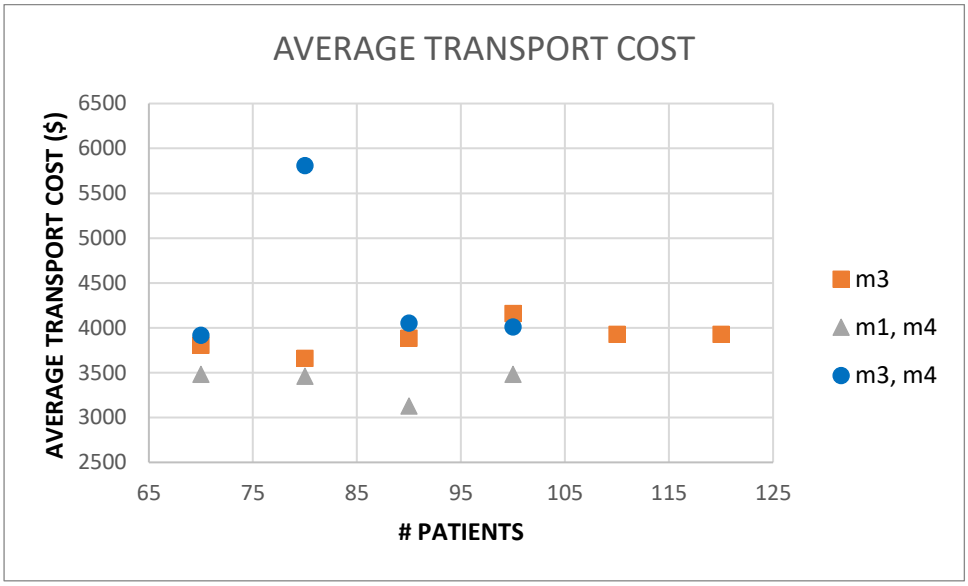

Figure 31: average transport cost in relation to demand level for the alternative medium sized networks

In this case, the network with m1 and m4 has the lowest transportation cost and it is followed by the network with m3 and lastly be the one with m3 and m4.

5.2.3 LARGE NETWORK

The same steps as in paragraph 4.3.1 will be followed for the bigger network, which includes manufacturing facilities m3 and m6 and was chosen as the optimal for the given demand profile of 125 patients. Again, this network was not fully utilized (m3 around 50%, m4 around 10%). In this paragraph the maximum number of patients that can be accommodated by this network will be evaluated.

Table 21: Total Cost per therapy, average return time and capacity utilization for each demand level – medium-sized network

Demand Maximization				
Established Facilities	Number of Patients	Total Cost per Therapy (K $)	Average Return Time	Average utilization (%)
m3 = 10 lines m6 = 10 lines	100	174.5	18.12	25% 34%
	110	160.7	18.14	35% 30%
	120	149.3	18.08	34% 37%
	130	139.5	18.23	38% 39%
	140	131.6	18.06	36% 47%
	150	124.3	18.11	49% 40%
	160	117.9	18.15	45% 50%
	170	112.3	18.21	48% 53%
	180	107.5	18.10	54% 53%
	190	103.1	18.14	59%

				53%
	200	99.1	18.17	57%
				62%
	210	95.5	18.09	68%
				56%
	220	92.3	18.13	66%
				65%
	230	89.4	18.10	68%
				68%
	240	86.5	18.19	69%
				74%
	250	84.1	18.10	74%
				74%
m3 = 12 lines m6 = 13 lines	260	81.8	18.10	61%
				62%

It should be mentioned that solver run out of memory after 250 patients in the network with m3 (10 lines) and m6 (10 lines) and after 260 patients in the network with m3 (12 lines) and m6 (13 lines)

In the following diagrams, the percentage of utilization of each manufacturing facility for each day and for each demand level is depicted.

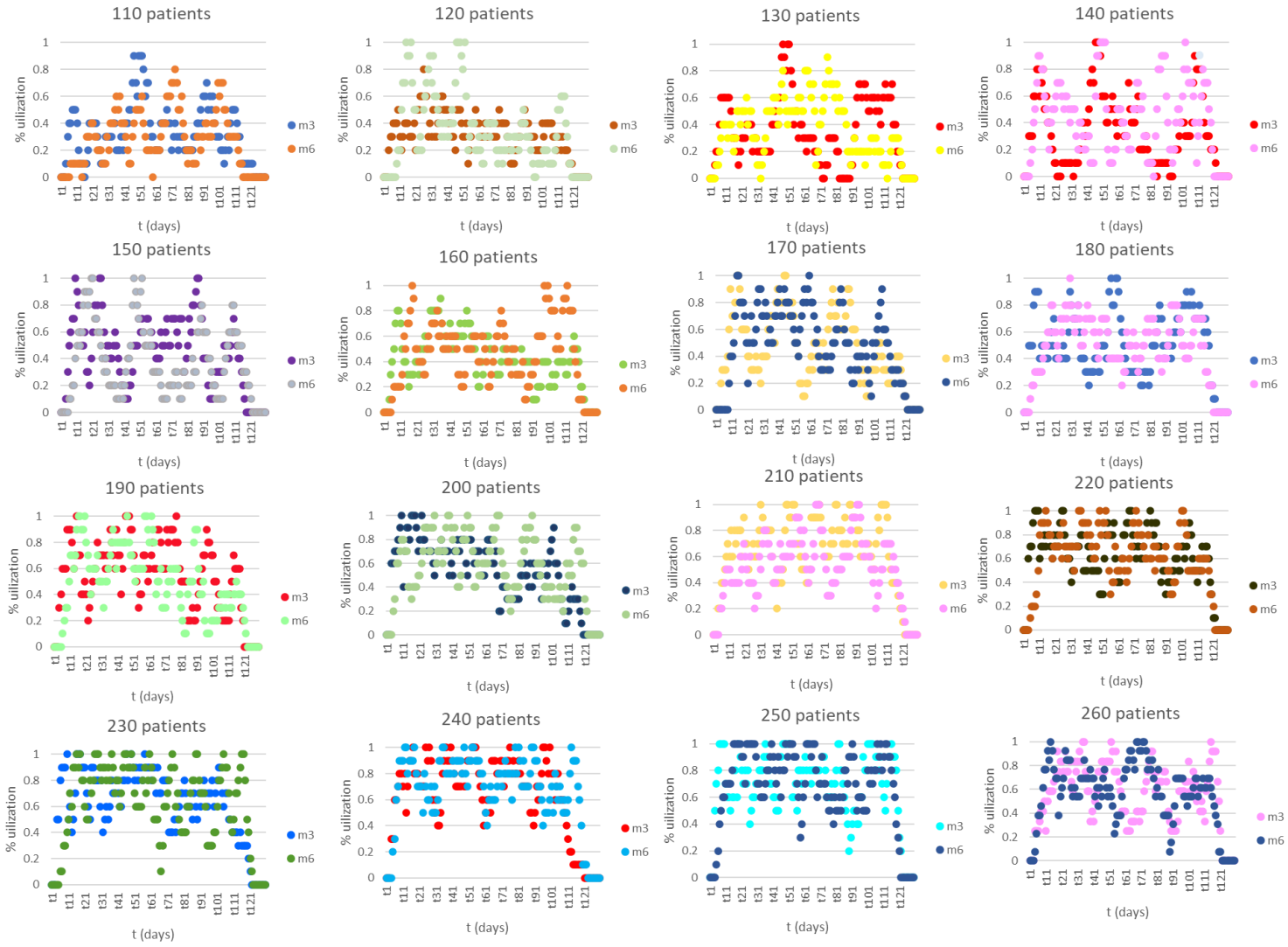

Figure 32: Bigger network – Capacity utilization for different demand levels

Also, there was constructed a diagram showing the relationship between the level of demand, percentage of capacity utilization and the cost per therapy.

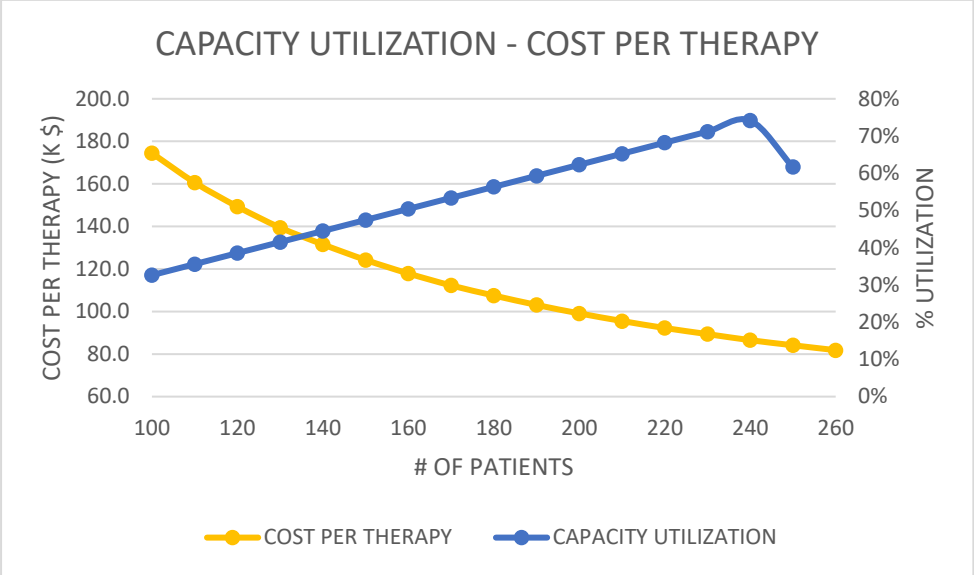

Figure 33: Capacity utilization and cost per therapy in relation to demand level – Bigger network

Again, it is observed that as the number of patient increases, the % of utilization also increases linearly and the cost per therapy decreases.

Subsequently, if the number of patients increased from 125 to 250 utilizing the existing m3 and m6 facilities, while allowing optimal allocation of patients, the cost per therapy would decrease from 143.7k$ [18] to 84.1k $. This is a very important decrease around 42%.

It is suggested that the manufacturing facility will be over designed to be able to accommodate fluctuations in the demand. We assume there was a 25% leeway in the design, that is set free now and the actual manufacturing facilities will have a capacity of 25 lines instead of 20. With this modification the maximum demand that the network can accommodate was not calculated because the solver run out of memory. There was only one solution for 260 patients.

Also, it is observed that average return time of therapies does not have a certain relationship compared to the number of patients, although it was suspected that the higher the demand the higher the return time. For all demand levels, return time is around 18 days with some fluctuations.

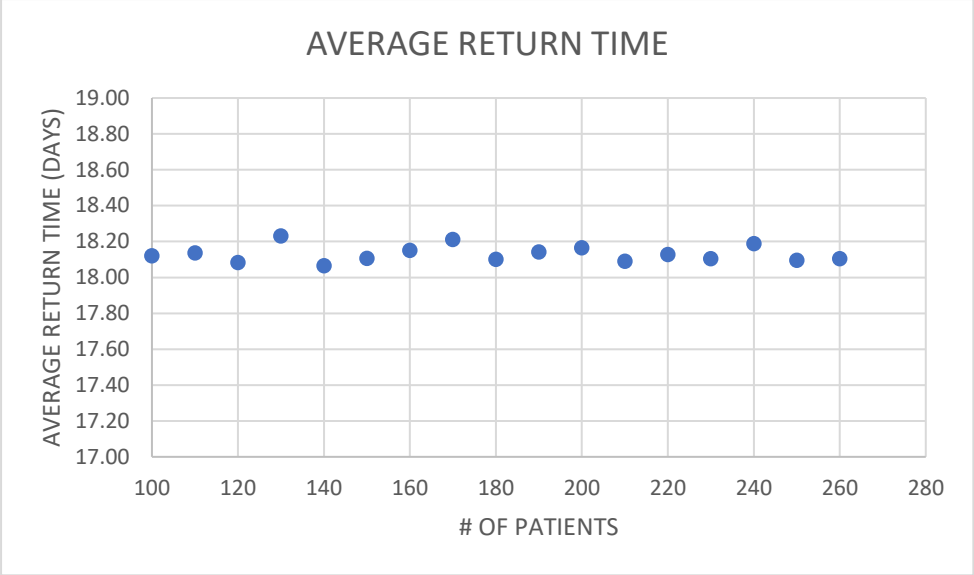

Figure 34: average return time in relation to demand level – bigger network

5.2.3.1 ALTERNATIVE NETWORKS

In this case it is assumed that facility m2 is already established and 20 lines of it are rented. It is noted that the cost is not depicted here, since new cost data of renting a facility instead of "building it" are not introduced in the model at this point.

Table 22: Average return time and capacity utilization for each demand level – alternative bigger network

Established Facilities	Number of Patients	Average Return Time	Average utilization (%)
m3=10 lines m6=10 lines	110	18.14	35%
			30%
	120	18.08	34%
			37%
	130	18.23	38%
			39%
	140	18.06	36%
			47%
	150	18.11	49%
			40%
	160	18.15	45%
			50%
	170	18.21	48%
			53%
	180	18.10	54%
			53%
	190	18.14	59%
			53%
	200	18.17	57%
			62%
	210	18.09	68%
			56%
	220	18.13	66%
			65%

	230	18.10	68%
			68%
	240	18.19	69%
			74%
	250	18.10	74%
			74%
m2 = 20 lines	110	17.99	36%
	120	17.99	36%
	130	18.09	39%
	140	18.03	42%
	150	18.11	44%
	160	18.11	47%
	170	18.11	50%
	180	18.18	53%
	190	18.11	56%
	200	18.12	59%
	210	18.10	62%
	220	18.13	65%
	230	18.06	68%
	240	18.00	71%
	250	18.05	74%
	260	18.11	77%
	270	18.08	80%
	280	18.10	83%
	290	18.14	86%

For each demand level return time and capacity utilization are similar between the two networks. However, the simple network with one manufacturing facility provides a solution for up to 290 patients while the more complex one can only up to 250. This is because by opening more facilities the network becomes more complex, binary variables and constraints increase, thus rendering the model infeasible sooner due to solver running out of memory.

The diagram below depicts the average return time in relation to demand level for the two alternative networks. There is not much variation in the values and all of them are around 18 days.

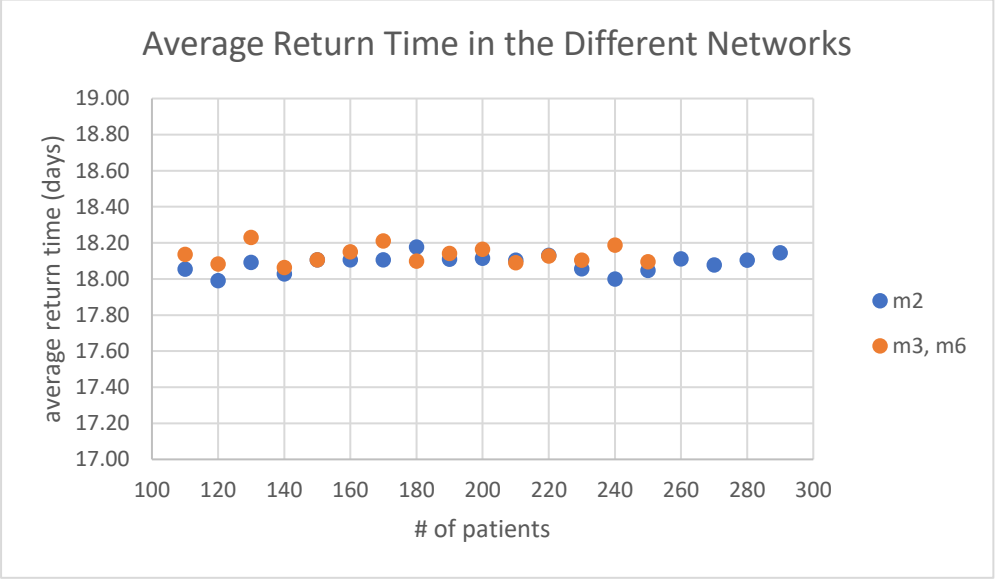

Figure 35: Average return time in relation to demand level for the alternative bigger networks

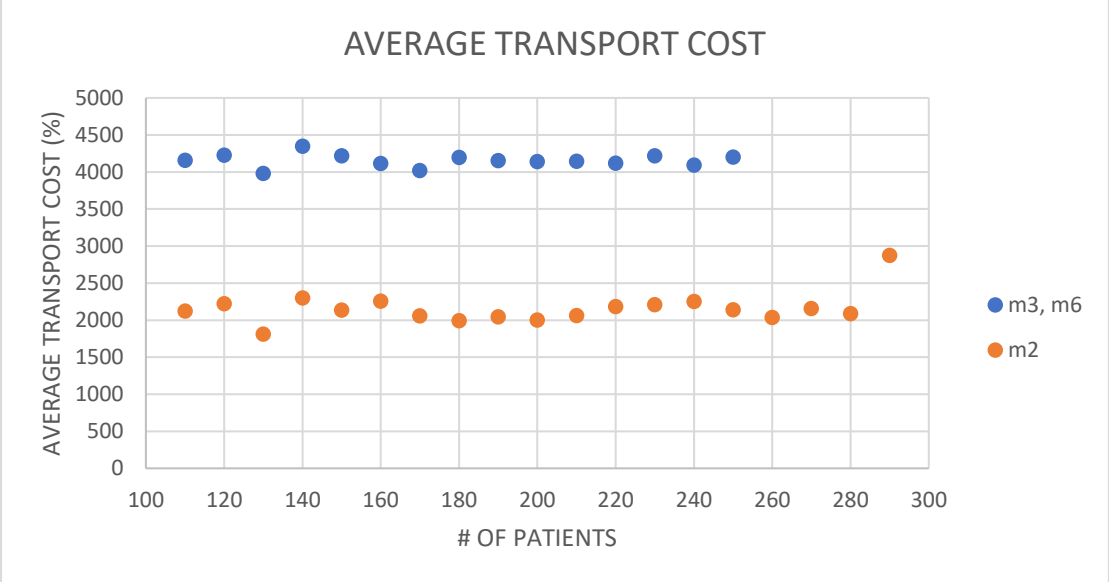

Figure 36: average transport cost in relation to demand level for the alternative medium sized networks

In this case, the network with only facility m2 has the lowest transportation cost. This was expected since facilities m3 and m6 have higher unit transport costs.

5.2.4 COMMENTS

In this section it has been proven how important it is to maximize the utilization of each manufacturing facility to minimize the cost. In all three different networks that were tested for the three demand levels it was proven that average cost per therapy was decreased by more than 40% compared to the results of the original model. Also, by analyzing the networks it was observed that the first node to get saturated is the manufacturing facilities. Because the market of CAR-T cell therapies is new and demand can be unexpected it is suggested to overdesign this unit to be able to absorb possible demand shocks. For this reason, it was assumed that in the nominal cases there was a 25% leeway that was set free in the rest of the scenaria. By testing this hypothesis, it is observed that capacity of the small network as a whole was increased by 17% and the capacity of the medium sized network by 30%. It was not possible to test this in the bigger network since solver run out of memory and could only produce results up to 260 patients.

Table 23: Average cost per therapy calculated by the original model, the demand maximization model with and without the leeway

Number of patients	**Original model**	**Demand maximization Model -25% leeway**	**Demand maximization model – no leeway**
20	172.6	172.7	172.7
50	142.7	82.6	82.6
125	143.7	142.6	71.3

These findings are depicted in the following diagrams.

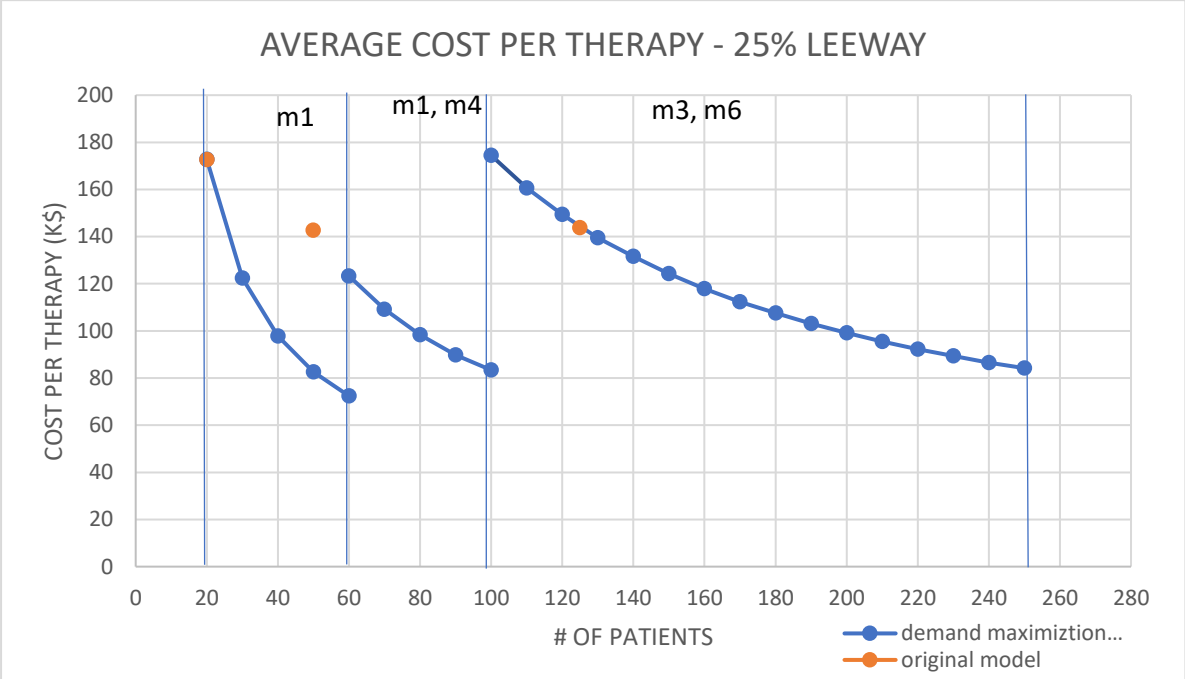

Figure 37: Average cost per therapy in relation to demand level in each supply chain network with 25% leeway

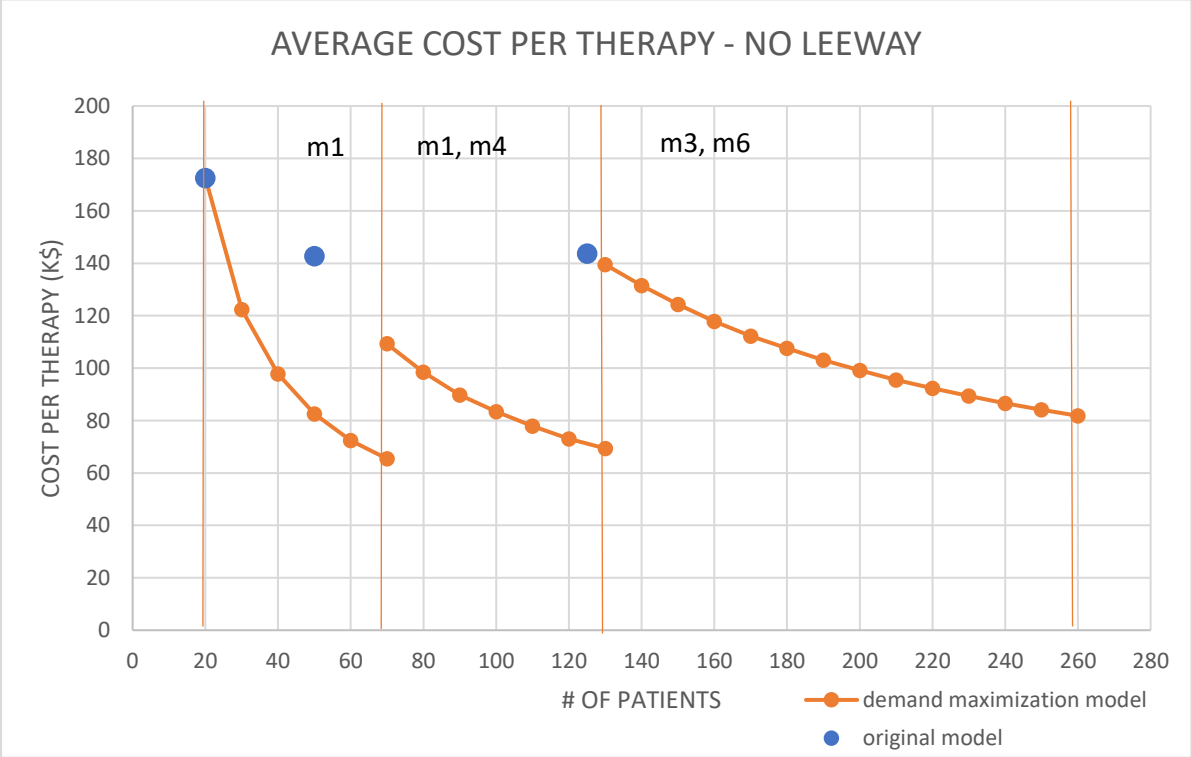

Figure 38: Average cost per therapy in relation to demand level in each supply chain network without the leeway

Furthermore, alternative networks with same capacity were tested to evaluate the possibility of renting part of other existing facilities. This can be a short-term solution before deciding which facilities to establish and with what capacity or a long term solution when expansion of the network will be needed due to higher demands. It was observed that networks with one manufacturing facility with larger capacity perform slightly better than more complicated networks with two or three facilities with smaller capacity. This is because computationally the problem becomes more difficult the more complex the network is.

5.3 WAITING TIME

All the above scenaria allocate the patients in an optimal way to the different leukapheresis sites. This might not be possible though, as these therapies are addressed to terminally ill cancer patients that will not be capable of travelling. In real life it would be more reasonable to have the patients wait in the hospital they originally arrive until a facility has free capacity to manufacture their therapies.

5.3.1 50 PATIENTS

Cost-wise as the usage ration of a facility increases the cost of the therapy is reduced, as it is proved. So, it has been seen that facility m1 can accommodate up to 60 patients (72,392.29$/therapy), but when the scenario with a randomized demand profile of 50 patients is tested, the model chooses to establish facilities m1 and m4, which almost doubles the cost of the therapy (142.736,456) [18]. This is because it is assumed that every patient is treated immediately and there are no delays between the processes. So, the moment a new patient arrives, and the manufacturing facility is full, a second one is established. In the following scenario it is assumed that patients can get in a “waiting list” for up to 14 days to reduce the cost. The waiting time will be before the leukapheresis procedure, so shelf-life problems are avoided. More specifically the arrival day of each patient is given by the randomized demand profile. Then, the algorithm calculates capacity in the manufacturing facility and if there is not available free line, the patient does not proceed to the leukapheresis procedure but remains in a waiting list. When a space opens up the patient get in for the leukapheresis and the rest of the supply chain is the same as the original model. In the scenario of 50 patients it is expected that model will choose to establish only m1 and indeed it does. The results are the following:

Table 24: Total Cost per Therapy and average return time if waiting time is allowed – randomized demand of 50 patients

MODEL	Established facilities	Number of Patients	Total Cost per Therapy (K $)	Average return time (days)	Average utilization (%)
WAITING TIME	m1	50	81.6	21.48	74%
OPTIMIZED ALLOCATION	m1	50	82.6	18.06	74%
SINGLE - OBJECTIVE	m1, m4	50	141.8	19.00	55% 12%

First of all, the main variable that must be checked is the total return time of therapies to ensure that it remains within a reasonable range. The average return time (21.48 days) is reasonable since some patients will need to wait and there will be a delay in their therapies. In the following diagram the total return time for each patient is depicted.

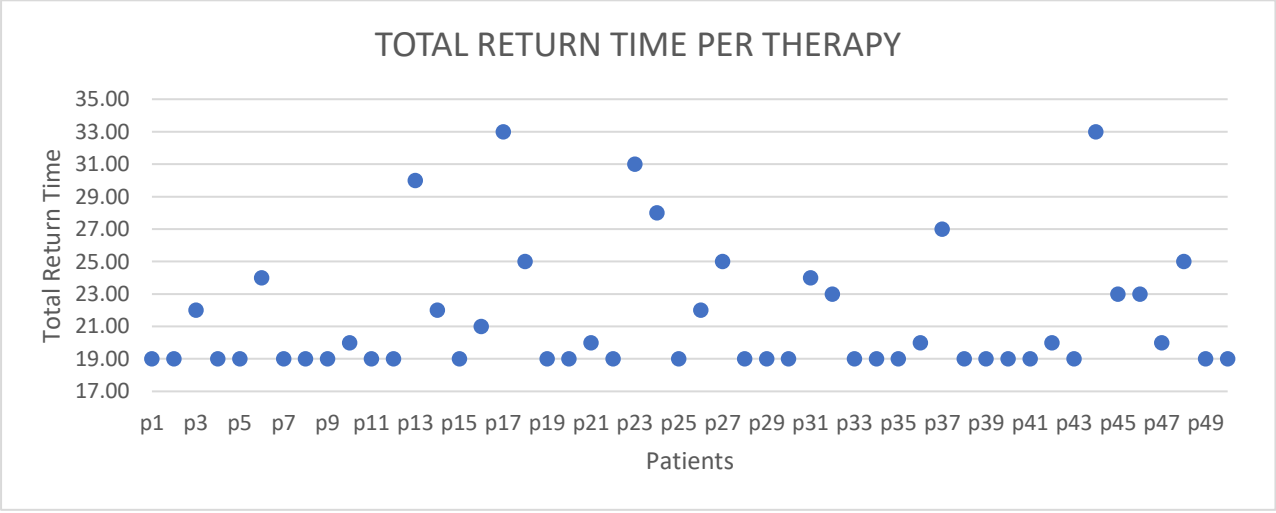

Figure 39: Total return time per patient if waiting time is allowed – randomized demand of 50 patients

It is observed that almost 54% of the therapies will be administered at 19 days, 34% will need to wait a week or less and 12% will delay from 7 to 14 days.

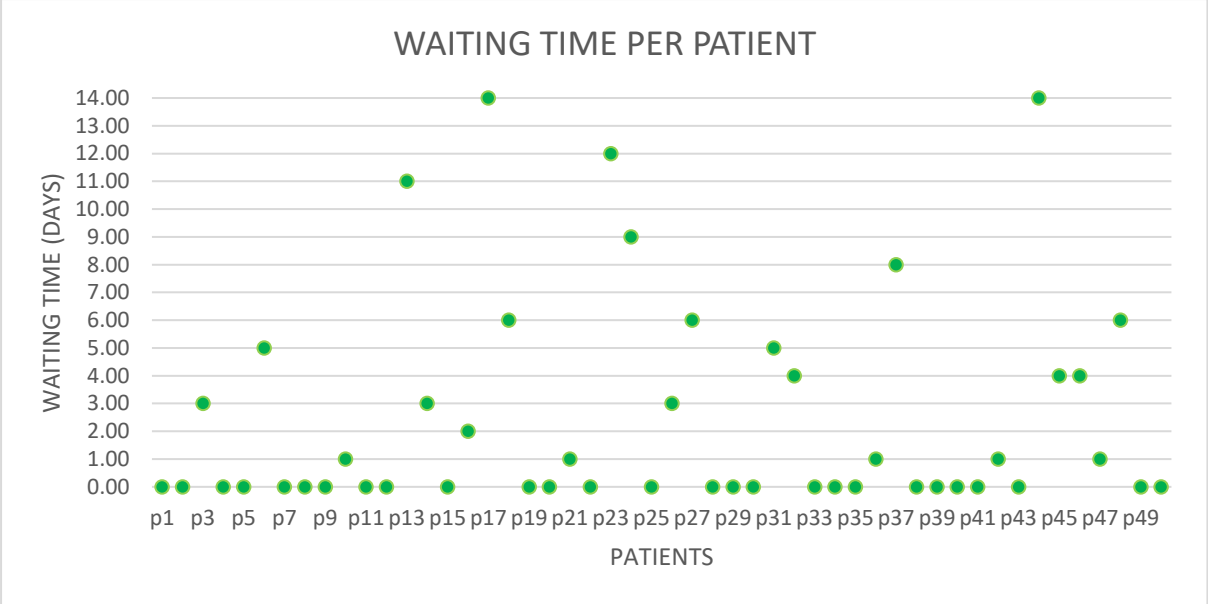

Figure 40: Total waiting time per patient– randomized demand of 50 patients

As far as the total cost per therapy is concerned, it is reduced from 142.8 k $ (single objective model without waiting time, [18]) to 81.6 K $ (single objective model with waiting time). These are very promising results since cost minimization is imperative if these therapies are to be produced commercially.

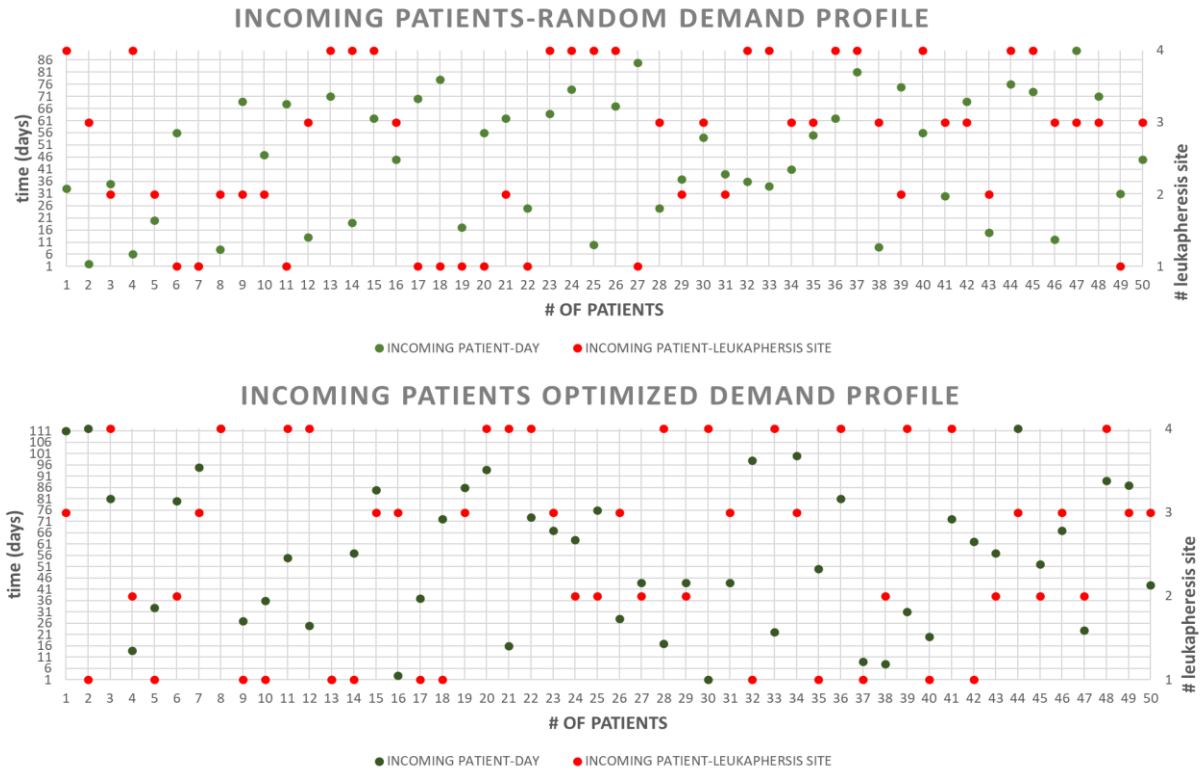

Figure 41: 50 incoming patients, randomized profile, and optimal allocation

5.3.2 125 PATIENTS

The same steps as in 4.4.1 were repeated for the randomized demand profile of 125 patient. The original model had chosen the establishment of m3 and m6 for this demand level, however utilization of the first facility was around 60% and of the second only 10%. The cost per therapy was as high as 142,6K $ [18]. The results from the new model are presented below:

Table 25: Total Cost per Therapy and average return time if waiting time is allowed – randomized demand of 125 patients

MODEL	Established facilities	Number of Patients	Total Cost per Therapy (K $)	Average return time (days)	Average utilization (%)
WAITING TIME	m3	125	82.5	19.56	74%
SINGLE - OBJECTIVE	m3, m6	125	142.6	19.00	57% 10%

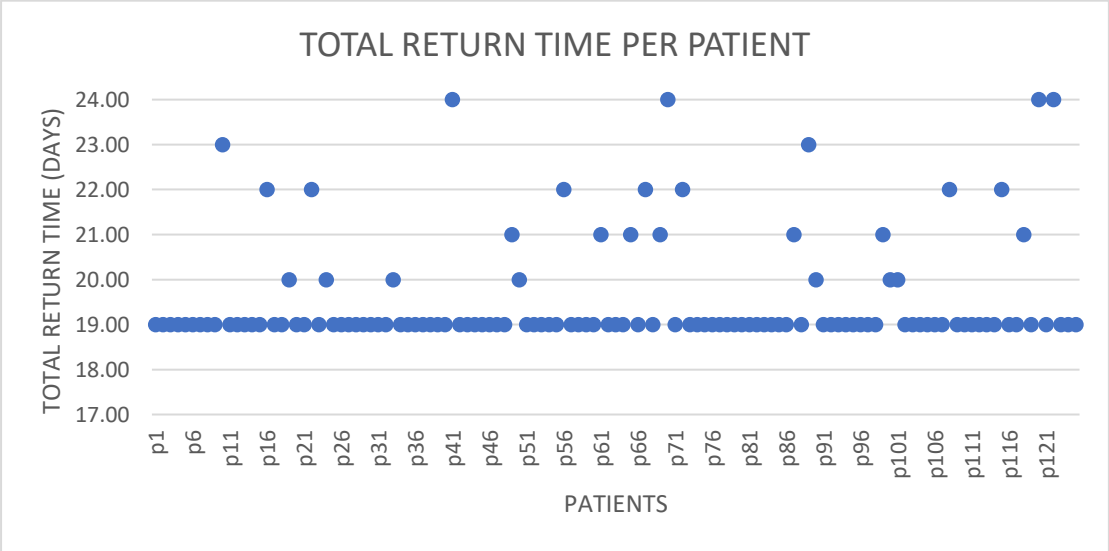

Figure 42: Total return time per patient if waiting time is allowed – randomized demand of 125 patients

It is observed that almost 78.4% of the therapies will be administered at 19 days, 16.8% will need to wait a 3 days or less and 4.8% will delay from 4 to 5 days.

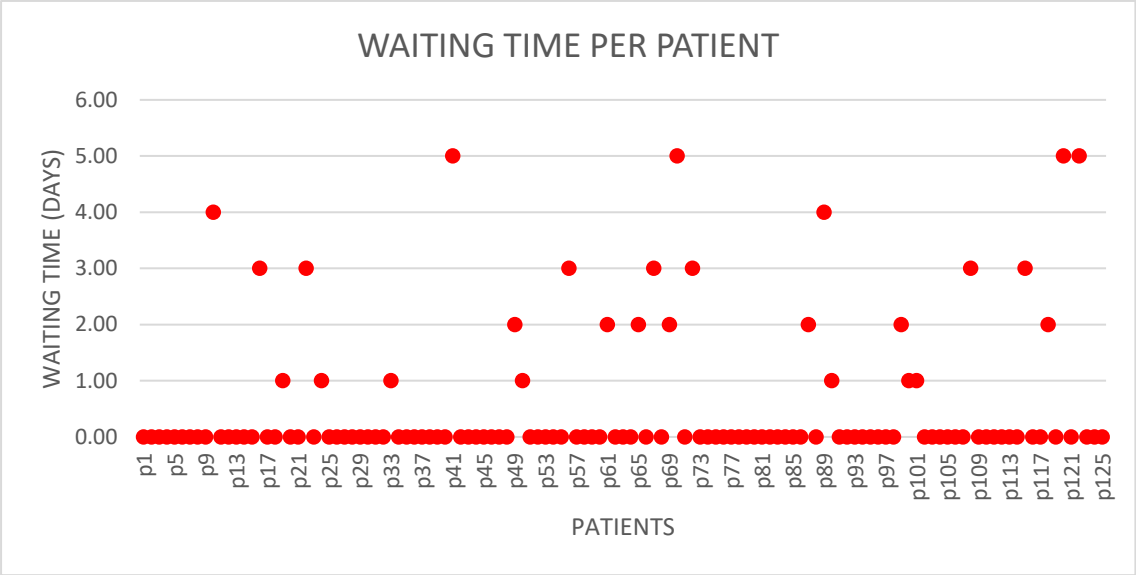

Figure 43: Total waiting time per patient– randomized demand of 125 patients

As far as the total cost per therapy is concerned, it is reduced from 142.6 k $ (single objective model without waiting time [18]) to 82.5 K $ (single objective model with waiting time). These are very promising results since cost minimization is imperative if these therapies are to be produced commercially.

5.3.3 COMMENTS

The addition of the waiting time in the model was a very important step, since it makes the network more realistic and a lot more cost-efficient. For both demand profiles that were tested the cost was almost 40% lowered compared to the original model and as the established manufacturing facilities were utilized at a higher ratio. What is also very important is that turnaround time of the therapy was not increased much for the vast majority of the patients. These findings suggest that the new model is significantly improved compared to the original one.

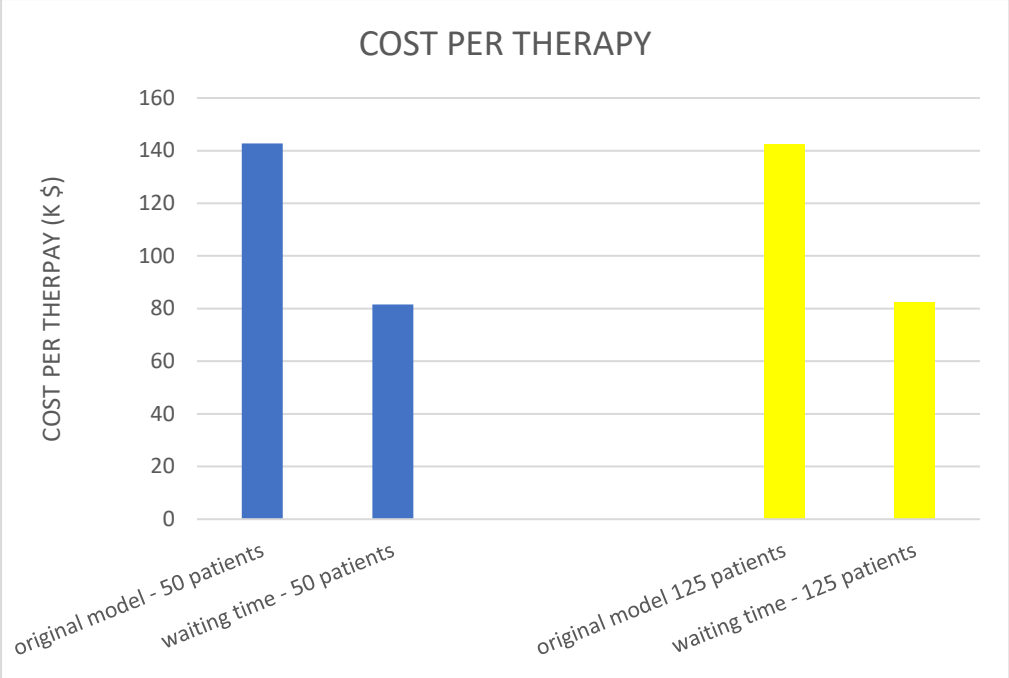

Figure 44: Reduction of total cost per therapy if waiting time is allowed

CHAPTER 6: CONCLUSIONS AND FURTHER RESEARCH

This thesis has addressed the increasing demand in CART cell therapies by improving a novel MILP model that optimizes the supply chain of their production and distribution. The scope of the analysis involves two main areas: multi-objective optimization for the selection of manufacturing facilities to be established and efficiency maximization of the proposed networks.

As far as the multi-objective optimization is concerned, the aim is to evaluate the trade-off between minimizing the cost and minimizing delivery time of the therapies. There are two methods evaluated: the weighted sum and the epsilon constraint. By comparing the two the epsilon constraint seems to be more efficient since the solution distribution is more uniform and many more pareto optimal points are calculated compared to the weighted sum method. The latter one, although very simple, gives reliable results but solutions are grouped around certain points and are not evenly distributed in the whole decision space.

The second part of the thesis aims to maximize utilization of each network to decrease cost by two different ways. The first one is by allocating in an optimal way the incoming patients to the different leukapheresis sites, to allow better patient scheduling in the manufacturing facilities. In that case, the user does not input a randomized demand profile to the model, rather only the total number of patients is given, and the model is responsible to allocate them. The new model is proved very efficient since average cost per therapy is reduced by almost 40% compared to the results of the original model. For 50 patients the original model suggests the establishment of m1 and m4 and the therapy has an average cost of 142.7 K$[18], while the new model utilizes only facility m1 and the cost is 82.6 K$. For 125 patients the original model establishes facilities m3 and m6 with an average cost per therapy at 143.7k$ [18], when the improved model uses facilities m1 and m4 or m3 alone with a cost around 80.1k$. It is mentioned that average return time in all the scenaria are around 18 days. The second method is by incorporating delays in the original model. It is true that optimal allocation of patients might not be always possible since the therapies are addressed to terminally ill cancer patients that will not be able to travel. For this reason, a waiting time has been introduced to the model. When the manufacturing facility is full and a new patient arrives, he/she is automatically put into a waiting list until an open spot opens and the patient proceed to the leukapheresis. With this procedure, the cost is again reduced significantly to 81.6K$ and 82.5K$ for the demand profiles of 50 and 125 patients respectively. All the above are very

promising results and since cost reduction is imperative if these therapies are to be produced commercially.

To conclude, the proposed approach is proven to be very efficient, however the model is not capable to produce results for bigger sized problems with much higher demand. Thus, the effect of combining it with a decomposition algorithm should be examined. Additionally, transition from the static model to a dynamic one should also be evaluated. Lastly, machine learning techniques used to forecast peak and off-peak times can also be helpful in rendering the model more realistic.

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