A SET COVER APPROACH TO BEAM ORIENTATION OPTIMIZATION IN INTENSITY MODULATED RADIATION THERAPY FOR TOTAL MARROW IRRADIATION

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Abstract

The purpose of this study is to investigate the use of the set cover problem (SCP) applied to beam orientation optimization (BOO) in intensity-modulated radiation therapy (IMRT). In addition, in this study IMRT is being used for total marrow irradiation (TMI), a form of total body irradiation (TBI), in preparation for bone marrow transplant. The BOO problem is modeled as a SCP and solved using existing algorithms and methods for solving the set cover. To evaluate the effectiveness of this approach, the selected beams are then used to generate treatment plans to evaluate for dose deposited into the target and organs-at-risk. The beam orientations and beam intensities are separately optimized in this approach. Using non-coplanar beams, there are 396 candidate beams from 36 equidistant beam angles in 11 equidistant couch positions. Beam selection criteria are driven by a pure greedy approach and three popular beam scoring methods. Following the selection of beams, a treatment plan is then generated for evaluation. This study demonstrates that the SCP approach is feasible for IMRT treatment planning of TMI.

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1 Introduction

With the advant of intensity-modulated radiation therapy (IMRT), doctors are now able to perform radiotherapy with greater success. IMRT allows for different beam delivery angles by rotating the gantry of the linear accelerator, the machine used to deliver radiation into the patient, about the patient. This gives the patient higher chances of having the target tumor removed and have a higher quality of life afterwards. Total marrow irradiation (TMI) is a necessary precursor to performing bone marrow transplants. TMI involves the eradication of the patient's existing bone marrow cells, while ensuring the critical organs are spared. The use of IMRT for TMI allows for the delivery of highly precise and controlled dosages of ionizing radiation to remove existing marrow. To fully exploit the benefits of IMRT, the number of beams and location of beams to deliver the dosages must be selected carefully, as it is one major factor in the impact of treatment quality. The problem of solving the beam orientation optimization (BOO) is part of the process of a larger overall optimization of generating treatment plans.

Since IMRT allows for the beaming of radiation from a 360° range around a patient's cross-section, it creates a large solution space from which to select the most optimal beams. Assuming all other movements are stationary except for the gantry angle, the beams sweep out in a coplanar fashion if the gantry is rotated. Beams that are obtained by the movement of more than just gantry angle are known as non-coplanar. Further, each beam can be thought of made of individual beamlets, each having intensities that can be controlled. This allows for very specific targeting of locations and dosage to be delivered. Since the beams will need to travel through healthy tissue in order to hit the target, much care must be taken in order to minimize the amount of healthy cells irradiated. By allowing non-coplanar beams to be utilized in the BOO problem for TMI, the solution space to select beams from is now even larger.

Our approach in solving the beam orientation optimization problem is to model it as a set cover problem (SCP). The SCP is a classical problem of selecting the minimal number of sets to cover all the elements in the "universe", where each set contains some (or none, or even all) of the elements. In this scenario, the human body is considered to represent the universe, the targets in the body are elements, and the beams to be the sets. The SCP is known to be NP-Complete (Karp, 1972), and not able to be solved optimially in polynomial time making it NP-Hard. Since NP-hard problems cannot be solved optimally in polynomial time, heuristics are often used to obtain a solution. By modeling the BOO into a SCP, it is hoped that existing algorithms developed to solve the set covering problem can be leveraged.

2 Literature Review

2.1 IMRT and Beam Orientation Optimization

The complexity of the beam orientation optimization problem has been addressed by several research groups. One method of selecting beam orientations is through the use of the beam-eye view (BEV). Unlike conventional radiotherapy where the selection is evaluated manually, the evaluation of the beam is performed by a scoring function. BEV is a common method used and extended upon in literature. This method measures the amount of target in the body that a beam can see. A measure of the amount of intersections between a beam's beamlets and target's voxels forms the basis for this metric.

$$r_{ijs} = \begin{cases} 1 & D_{ijs} \geq \epsilon \\ 0 & otherwise \end{cases}$$

Where r_{ijs} is a binary variable representing an intersection of beamlet i and voxel j in structure s, when the dose deposition is greater than a threshold ϵ. Scoring an individual beam would be the summation of the number of beamlet-voxel intersections r_{ijs}.

$$F_{BEV}(\theta) = \sum_{s=1}^{T} \sum_{j=1}^{v_s} \min \left\{ 1, \sum_{i \in \mathcal{B}_\theta} r_{ijs} \right\}$$

The BEV concept was extended by Pugachev and Xing (2001a,b, 2002) into the pseudo beam's-eye view (pBEV). It utilizes the scoring function:

$$F_{pBEV}(\theta) = \frac{1}{v_s} \sum_{s} \sum_{j} \left(\frac{\overline{D}_{js\theta}}{T_s} \right)^2$$

This function is used to score the beam θ. This scoring function scores each beam on the assumption that it is the only beam in the solution. The numerator $\overline{D}_{js\theta}$ is the maximum dosage delivered to voxel j in structure s by beam at θ. However, this function still relies on other methods to perform the beam selection, usually on the basis of trial-and-error and past experience. Utilizing the beam's eye view dosimetic (BEVD) concept developed in Pugachev and Xing (2001a,b), the results of beam selection are used to evaulate effectiveness via an objective function. (BEV) was originally utilized for treatment planning by allowing oncologists to validate beam entry angles by taking a view of structures hit. BEVD is a measurement method in order to rank beams, creating a priori knowledge to feed into optimization. Utilizing this prior knowledge, the search space is reduced by eliminating the poor beam angles. From this reduced space, different configurations of beams are compared and scored to select the best configuration.

Another extension to BEV is the target-eye view (TEV). TEV takes into account the critical structures that overlap with the target. When an overlap does occur, it is called a hit; a distal hit refers to the critical structure behind the target in the BEV, whereas a proximal hit refers to critical structures in front of the target. A marginal hit is when the distance between a critical structure and the target is less than the beam's penumbra. For each type of overlap, a collision score g is assigned and for every critical structure s, a relative critical score c_s is assigned.

$$F_{TEV}\left(\theta\right) = \sum_{s=T+1}^{S} \sum_{j=1}^{v_s} \sum_{m=1}^{G} y_{ijs} c_s g_m$$

Beams that have a high amount of overlap will score lower, thus be considered to be of poorer quality.

Mean organ-at-risk data (MOD) is a scoring function that emphasizes impact on critical structures. A beam is scored by first obtaining a treatment plan from a single unmodulated beam, shaped to the BEV of the target. The prescribed dose in this plan is 1.8 Gy, resulting in beamlet intensities **x**. The plan is then normalized so that the mean dose is 2.0 Gy, which yields a vector $\hat{x}$. The MOD score would then be

$$F_{MOD}\left(\theta\right) = \frac{1}{\sum_{s=T+1}^{S} v_s} \sum_{s=T+1}^{S} \sum_{j=1}^{v_s} D_{ijs} \hat{x}_i$$

Another method of performing beam orientation optimizing is the use of mixed integer programming (MIP), as examined by Lee et al. (2003, 2006); Yang et al. (2006). A MIP formulation of the BOO problem uses a binary variable to determine if a beam is selected from a set of all possible beams. The nature of the model presented allows for many possible objective functions. Lee et al. (2003) chose to minimize the weighted sum of excess dose to the PTV and total dose to OARs. The objective was constrained by a need to ensure dosage delivered to target was medically acceptable, that the dosage was between lower and upper limits of each structure, a maximum number of beams to use, and the maximum dosage from a beam.

Combining the fluence optimization and beam optimization into a single mixed-integer program was examined by Lee et al. (2003, 2006). Still formulated as a MIP, two decision variables are utilized: binary 0/1 variables to capture ”on“ or ”off“ for each field, and continuous non-negative variables to represent fluences. Five different objective functions were presented, all of which are required to satisfy the same set of constraints. Each objective function highlights a specific portion of the treatment plan for optimization. Since all the objects are subjected to the same constraints, they will all produce a feasible treatment plan.

The MIP presented by Yang et al. (2006) is formulated to minimize the weighted sum of the average doses to the OARs, subjected to constraints on the target receiving an acceptable dosage, and a limited number of beams. The beams are selected from the pool that was previously defined. Originally formulated as a mixed nonlinear integer programming problem, it was reformatted into a mixed linear integer program to compute in an acceptable time frame. This scoring function has removed consideration of the dosages delivered to target, instead it choses to focus on the dose received by OARs.

Formulated as a MIP, this approach relies on a preselected pool of beams from which the optimal set can be selected. Thus the quality of the selected beams are governed by the rules which defined the beams in the pool. These approaches integrate the BOO and FMO problems to be solved simultaneously. Pure integer programming (IP) methods have also been examined (D’Souza et al., 2004). Due to the complexity of IP, prescoring beams is an approach used to improve performance. One such method is to prescore the beams on an individual basis, using beam scoring methods mentioned above. However, the binary requirements of the decision variables in these approaches results in poor performance.

Most clinical applications utilize some form of heuristic to generate a possible plan in acceptable time. Other methods rely on trial-and-error, or the clinician's experience. The goal is to obtain a beam orientation optimization algorithm that is performed in an acceptable timeframe (hours), and produces results that are acceptable from a medical perspective.

2.2 Set Cover Problem

Set cover problems have been determined to be NP-Hard, a class of problems that are not solvable to optimality in polynomial time. Thus heuristics are used to obtain a solution within a reasonable time. Most heuristics follow the concept of the greedy algorithm. The algorithm introduced by Chvatal (1979) has become the basis for many works. Chvátal proposed an algorithm that was greedy in nature, and able to deliver a near-optimal solution. It is a recursive algorithm where an additional set is added each iteration until all data elements have been covered. It selects the set from a list of finite sets which will maximize the ratio of elements covered by the set to cost of the set, hence maximizing number of elements covered per unit cost giving rise to the "greedy" name.

Another form of heuristic that could be applied is local search as proposed by Mulsiu (2006). It is proposed that a local search with a tabu list, along with a upperbound of selected sets to guide neighborhood selection would improve performance. The algorithm was shown to be effective for the unicost set cover problem, wherein all elements have equal weight. The neighborhood was defined using two operatorions: adding a set *S* (which is not in C) to the family of sets in C; and removing a set S from C. The neighborhood is then further restricted through the use of an upper bound. The upperbound *u* acts as a restriction adding a set to the solution by only allowing if the number of sets in the current solution is less than *u* - 1. The upperbound is calculated from the first legal solution, and all subsequent solutions that are better than the current. The cost function defined as

$$C = \overline{V}_{\Theta^{(i)}} + |\Theta^{(i)}|$$

Where $\overline{V}_{\Theta^{(i)}}$ is the number of voxels unhit by beam solution Θ, and $\Theta^{(i)}$ is the solution in iteration i.The objective is to minimize the cost function. The tabu list was defined to contain the family of operators for the sets to be added. It was found empirically that the optimal length of the list is a function of the number of sets produced by the greedy algorithm.

Another type of heuristic presented by Bautista and Pereira (2007) is known as greedy randomized adaptive search procedure (GRASP). The GRASP algorithm presented is a two phase heuristic comprised of a constructive phase and local search phase. In the constructive phase, an initial solution is obtained through the use of a random greedy heuristic. Specifically, it is a modification of the greedy heuristic wherein selection of a set is random instead of by score. A local search is then performed in an effort to obtain a solution that is better than the generated one. If the second phase does not produce a better solution, the algorithm may return to phase one in an attempt to generate a better solution. This process continues for a predetermined number of iterations, where the best solution obtained is presented at the end.

3 Model

Given a set of targets $\mathcal{T}$ to hit and a set of OARs $\mathcal{S}$ to minimize dosage to, we want to select Θ set of beams to use. Theses beams will selected from $\mathcal{B}$ candidate beams. We will select *k* beams such that $\Theta \in \mathcal{B}^k$. Each structure $s \in \mathcal{S} \cup \mathcal{T}$ has a finite number v_s of voxels. Letting a black-box function that scores the beam θ be $F(\theta)$, we want to obtain the best set of beams.

$$\begin{aligned} \min \quad & \mathcal{F}(\Theta) = \textstyle\sum_{\theta \in \Theta} F(\theta) \\ \text{subject to} \quad & \Theta \in \mathcal{B}^k \end{aligned}$$

The analogous set cover problem would have the universe $\mathcal{U} = \{u_1, u_2, \ldots, u_n\}$ consisting of targets and OARs $\mathcal{T} \cup \mathcal{S}$. The goal is to obtain a solution set $\mathcal{C} = \{b_1 \cup b_2 \cup \ldots \cup b_k\}$ from a set of beams $\mathcal{B}$ that covers all $\mathcal{T}$.

4 Methodology

The BOO problem is modelled into a set cover problem by modelling the target structures' voxels into elements of the universe. Likewise, the beams are modelled into the sets. For the (TMI) problem, gantry angles are in increments of 10°, resulting in 36 possible beam angles. The couch is allowed to translate on the patient plane (Z-axis) in units of 10. This results in 11 couch positions for the upper body. A total of 396 beams are in the pool available to be used. All programming and data were performed using MATLAB 2008.

The process of obtaining the treatment was broken down into these discrete steps:

1. Model the BOO as SCP
2. Solve the SCP
3. Map solution back to beams
4. Solve the FMO

The resulting output is the treatment plan, including a dose volume histogram for evaluation. All tasks were performed on a Penguin Computing Beowulf cluster, using the MATLAB distributed computing function.

The target for TMI is a structure known as hemiPTV, with all other organs and structures in the body considered to be organs-at-risk OAR. The target prescription dose is 12 Gy for 95% of the target volume. All other organs are to receive as minimal dosage as possible.

The FMO model presented by Aleman et al. (2008) is solved using a projected gradient function previously developed. The function accepts weighting parameters for structures and the minimal improvement threshold to continue iterations for finding the optimal fluence. Different weighting parameters, improvment thresholds, and organ penalty thresholds were evaluated.

$$F_s\left(z_{js}\right) = \frac{1}{v_s}\left[\underline{w}_s\left(T_s - z_{js}\right)_+^2 + \overline{w}_s\left(z_{js} - T_s\right)_+^2\right]$$

Where F_s is a convex penalty function for cumulative dose z_{js} received by voxel j in structure s. This function normalizes using the total voxels v in structure s, equating all the structures, regardless of how large or small it is. The parameters w_s and T_s represent the weighting factor for over/underdosing and target dose for structure s respectively. Convexity is assured with the power of over/underdosing > 1, and only in effect if the difference is positive. The cumulative dose is calculated from the sum of radiation deposited in voxel j by beamlet i of beam θ. Taken across all beams and voxels, the cumulative dose is dose deposition coefficient D_{ijs} multiplied by beamlet intensities x_i.

$$z_{js} = \sum_{h=1}^{k} \sum_{i \in \mathcal{B}_{\theta_h}} D_{ijs} x_i \qquad j = 1, \ldots, v_s, s = 1, \ldots, S$$

5 Results

The greedy algorithm was applied to four cases of the set-cover problem. In each case, the patient data was from the same single source. The solutions obtained through the greedy algorithm were then submitted to a FMO solver using a projected gradient. The target for TMI is the "hemiPTV" structure, which is an omnipresent target in the body, consisting of 331,715 voxels.

5.1 Set Cover

The adjacency matrix was created by establishing a threshold ϵ, which a dose deposition coefficient must be greater than to be considered a hit. Two ϵ values were considered: 0.1 and 0.5. If a beamlet's D_{ij} is greater than the threshold, it is considered a "hit". By taking the maximum D_{ij} values for a beam across all beamlets on the target structure, the amount of hit voxels for was established. This forms the adjacency matrix, which represents the universe of elements and sets for which to solve the set cover problem. See Table 1 for details. The matrix consists only of binary elements depicting hit or no hit for beam i on voxel j.

Case	Multicover	Threshold	Average number of voxels covered per beam	Time to create matrix (sec)
1	5	0.1	277,364	396.8405
2	10			
3	5	0.5	204,031	396.2816
4	10			

Table 1: Cases examined and adjacency matrix details

Each case is a different set of parameters as input for the SCP algorithms to solve. All cases utilize the same patient and beam information, with only the thresholds differing. This is not to be interpreted as four different patients, rather, it is one patient with four different inputs into the solving mechanisms

5.2 Beam Orientation Optimization

The set-cover problem was solved as a multicover problem. This requires each element to be covered k times. The beams were scored according to the methods presented in section 2.1. Each beam scoring method and SCP algorithm were paired to obtain the results shown in Table 2.

	Chvátal		BEV		pBEV		MOD	
Case	Beams	Time (sec)	Beams	Time (sec)	Beams	Time (sec)	Beams	Time (sec)
1	24	16.2	80	17.4	143	28.2	265	49.5
2	54	32.1	148	29.0	232	42.9	297	57.2
3	31	19.8	163	31.2	230	42.0	388	69.4
4	77	43.8	279	49.0	245	44.1	395	71.5

Table 2: BOO results using Greedy Algorithm without cutoff, all performed on a Beowulf cluster

The greedy algorithm continues to add additional beams until all voxels have been covered at least k times. This leads to the high number of beams that are selected from BEV, pBEV, and MOD scoring. The high number of beams suggests that the algorithm is continuously looking for additional beams in order to statisfy the k cover. In order to generate an acceptable solution for treatment purposes, an incremental cutoff threshold was implemented. After k^{th} beam is selected, if the improvement in percentage of voxels being covered k times falls below the threshold, then the algorithm stops. The same cases and beam scoring methods from Table 2 were reapplied with a cutoff improvement of 0.2%, which is only in effect after 90% of elements have been covered k times. The results obtained with the cutoff in Table 3 show an immense reduction in number of beams selected.

	Chvátal		BEV		pBEV		MOD	
Case	Beams	Time (sec)	Beams	Time (sec)	Beams	Time (sec)	Beams	Time (sec)
1	6	6.88	59	14.2	13	7.20	49	15.8
2	11	7.01	69	17.0	26	11.2	54	16.1
3	23	11.0	61	15.6	20	9.12	49	15.8
4	22	11.0	69	16.0	37	14.8	64	18.4

Table 3: BOO results using Greedy Algorithm with an required improvement threshold of 0.2% , all performed on a Beowulf cluster

5.3 FMO

Following the selection of beams to solve the multicover SCP, the selected beams were then submitted to a FMO solver. The solver optimizes the bixels of the selected beams to create the treatment plan. In the case of BEV, pBEV, and MOD scoring, due to the large number of beams selected only the beams selected with improvement threshold in effect are optimized. However, the results from Chvátal's method without cutoff are sufficiently low enough to optimize.

	Chvátal		BEV (cutoff)		pBEV (cutoff)		MOD (cutoff)	
Case	FMO	Time	FMO	Time	FMO	Time	FMO	Time
1	14,200.7	212	38,838.5	333	26,429.3	57.9	36,813.8	108
2	15,792.2	712	26,798.6	448	20,937.0	332	24,544.6	315

Table 4: FMO Results of Greedy-based solutions, all obtained with a improvement change cutoff of 0.001. Time in minutes

Due to hardware and software limitations and issues, FMO results were unable to be obtained for cases 3 and 4. Section 7 details how this will be addressed. The result of the projected gradient function outputs the bixels of the beams selected to use. The bixels are then used to create dose volume histograms (DVH) to provide a visual intrepretation of quality. Figure 1 is representative of the DVHs obtained in this investigation. The remaining DVHs are in Appendix B

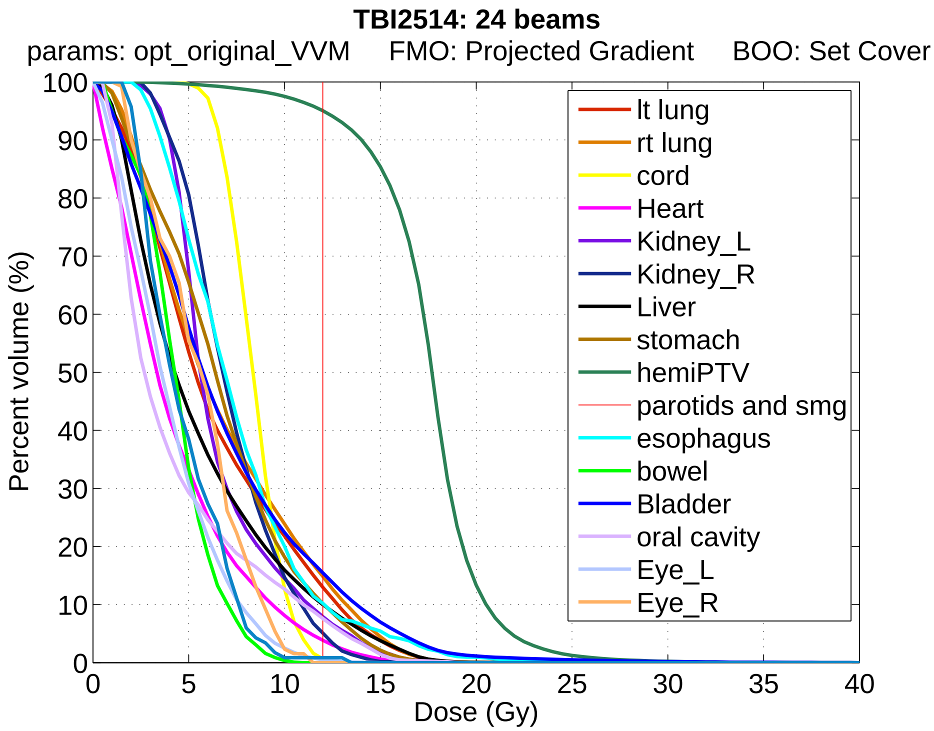

Figure 1: The DVH showing the result of FMO solver, case 1 based on Chvátal

6 Discussion and Conclusion

The use intensity-modulated radiation therapy allows for new freedom in treatment planning for radiotherapy. For purposes of total marrow irradiation, it can allow a more precise targeting and delivery of radiation to increase the chances of successful treatment and higher post-treatment quality of life. While opening up new possibilities in treatment planning, IMRT has also introduced a new level of complexity. IMRT brings the complexities of beam angle and couch position selection, followed with fluence map optimization. TMI differs from site-specific treatments in having a large continous omnipresent target that spans the entire body. In exploring the use of IMRT for TMI, the complexities of both problems are now coupled.

By modelling the BOO problem as a set-cover problem, we have inherently removed physical "knowledge" about the beams' attributes that clincians often use. In exchange, the sets are scored based on some methods presented in Aleman et al. (2007). The nature of TMI results some of the beam scoring methods to be unfeasible, particularly scoring methods which require knowledge of the target's location relative to the beam origin and other structures in the body. This study examined one set-covering "score" and four beam scoring methods and the quality of the beams selected. Each scoring method utilized in a greedy manner shows different improvement gradients.

Using just Chvátal's greedy method to solve the set-covering problem, the selected beams form acceptable treatment plans (See Figure 1 on page 14). Chvátal's method does not incorporate any additional knowledge, unlike the beam scoring methods, it merely selects the best beams for hits on the target. Pseudo beam's-eye view and mean OAR dose take into consideration the other structures that are hit for any beam selected. Thus leading to a tendency to select beams with lower impact non-targets. For TMI planning purposes, it is crucial to recall that hemiPTV is a omnipresent target. Scoring mechanisms that ignore this fact could potentially generate a poor treatment plan, as demonstrated with the pBEV and MOD results. As a beam solution attempts to minimize its impact on non-targets, it will consequently minimize its hits on the omnipresent hemiPTV. Due to hemiPTV's omnipresent nature, it renders TEV scoring to be unusable. The inability to determine what constitutes a proximal and distal hit in relation to the target, which is the crux of the scoring method, prevents the use of target's-eye view scoring.

The results of applying the beams selected in cases 1 & 2 into the FMO yields treatment plans that are at, or very close to, the target dose of 12 Gy to 95% of hemiPTV. All the scoring methods select beams that can result in at least 80% of the target receiving the prescribed 12 Gy, however the same beams can cause the dosages received by OARs vary extremely. Results from using Chvátal's greedy method show that dosages received by the OARs falls rapidly, compared to BEV, pBEV, and MOD. Using the target dose of 12 Gy as a indicator, it can be seen that the volume receiving that dosage for OARs is much higher in BEV, pBEV, and MOD, compared to Chvátal. For cases 1 & 2, it can be clearly seen that none of the OARs in Chvátal scoring cross 12 Gy greater than 20%, whereas all other scoring methods show at least two OARs crossing 12 Gy greater than 30%. Due to a lack of knowledge in the application of IMRT for TMI, it is extremely difficult to quantify an acceptable OAR dose. However, the prevailing principle of minimizing healthy tissue irradiation leads to the conclusion that Chvátal's greedy algorithm, without any beam scoring, produces superior results compared to when beam scoring is applied.

This approach has demonstrated the possibility of utilizing the set cover problem to assist in the treatment planning of TMI. However, this is a single study demostrated, using only one set of static patient data. Further work is required to determine the feasibility of this approach for IMRT planning in TMI.

7 Future Work

This study examined the feasibility of using a set cover approach to solve the beam orientation optimization problem. Further work is required in order to evaluate its effectiveness. For this study, the only type of treatment being considered is TMI. An evaluation of this approach in other types of treatments, such as site-specific treatments, would provide a more conclusive viability of using this set cover approach.

As noted in Section 5.3, FMO results for cases 3 & 4 still have not been obtained. Due to hardware issues, namely the lack of memory available to use the projected gradient function, and software, MATLAB's jobmanager failing to distribute jobs correctly, attempts to execute the function have resulted in running out of memory and system failure. Once these issues have been resolved, cases 3 & 4 can have their dosages calculated.

Specific to the greedy algorithm, the beam scoring methods which drive the algorithm should be examined. A combination of different scoring methods to create a new beam scoring metric. For purposes of TMI, a metric that incorporates the target voxels hit and a "penalty" for OAR hit could yield a better selection algorithm. Preliminary work of modified beam scoring metric using the ratio of Chvátal's set scoring to IMRT beam scoring shows much improvement in the number of beams selected (without cutoff) compared to the pure BEV, pBEV, and MOD methods.

	BEV	BEV (cutoff)	pBEV	pBEV (cutoff)	MOD	MOD (cutoff)
Case	Beams	Beams	Beams	Beams	Beams	Beams
1	27	8	24	9	43	19
2	58	13	55	13	70	26
3	34	13	33	22	47	37
4	79	23	79	27	86	52

Table 5: Preliminary results using the greedy algorithm scored by a ratio of Chvátal's set scoring to beam scoring. All times in seconds, cutoff is a 0.2% improvement

The greedy algorithm is just one method of solving the set cover problem. The local search and GRASP approaches were examined for this study. However, the performance of the greedy algorithm implemented was sufficient to generate multiple beam solutions to evaluate. Future work can examine using these approaches to refine the beam solution obtained through greedy method.

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A Algorithms

The algorithms presented here are the pseudo code description of the functions implemented in MATLAB.

Algorithm 1 Code to generate adjacency matrix

for all $\theta \ in \ \mathcal{B}$ **do**
    for all $i \in$ totalVoxels **do**
        find maximum D_{ij}
        if max$(Dij) \geq \epsilon$ **then**
            voxel i is hit by θ
        end if
    end for
end for

Algorithm 2 Solving the set-cover problem

U be the universe of uncovered elements X
if $k > 1$ **then**
    find elements X covered $< k$ times
    add sets S, where $X \in S$, to solution F
end if
while $U \neq \emptyset$ **do**
    select S that maximizes $|S \bigcap U|$
    $F \leftarrow S$
    U = U - S
end while
return F

Algorithm 3 Calculating BEV

for all beam $\theta \in \mathcal{B}$ **do**
    for all structures $s \in$ T **do**
        $r_{ij} = \sum |D_{ij}| > \epsilon$
    end for
    $\sum$ min$\{1, r_{ij}\}$
end for

Algorithm 4 Calculating pBEV

for all beam $\theta \in \mathcal{B}$ **do**
  for all structures $s \in$ T **do**
    find voxels intersected by beamlet i
    set x_i such that all target voxels crossed get at least the prescribed dose
    find minimum ratio such that all non-target voxels hit are below threshold (2 Gy)
  end for
  reduce x_i by ratio
  score = calculate dosage with intensities x_i
end for

Algorithm 5 Calculating MOD

for all beam $\theta \in \mathcal{B}$ **do**
  find intensities x with PTV prescribed dose of 1.8 Gy
  normalize to $\hat{x}$ so that PTV is now receiving 2.0 Gy
  for all structures $s \in$ T+1 **do**
    calculate dose delivered by $\hat{x}$
  end for
  sum dose for non-PTV structures
end for

B Dose Volume Histograms

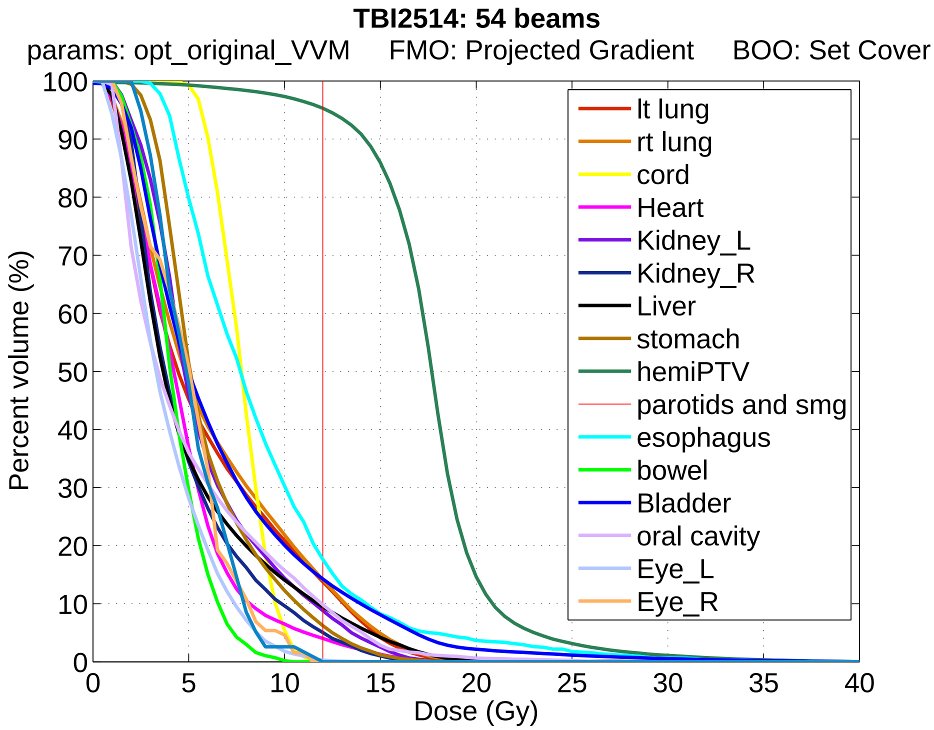

Figure 2: The DVH showing the result of FMO solver, case 2 based on Chvátal

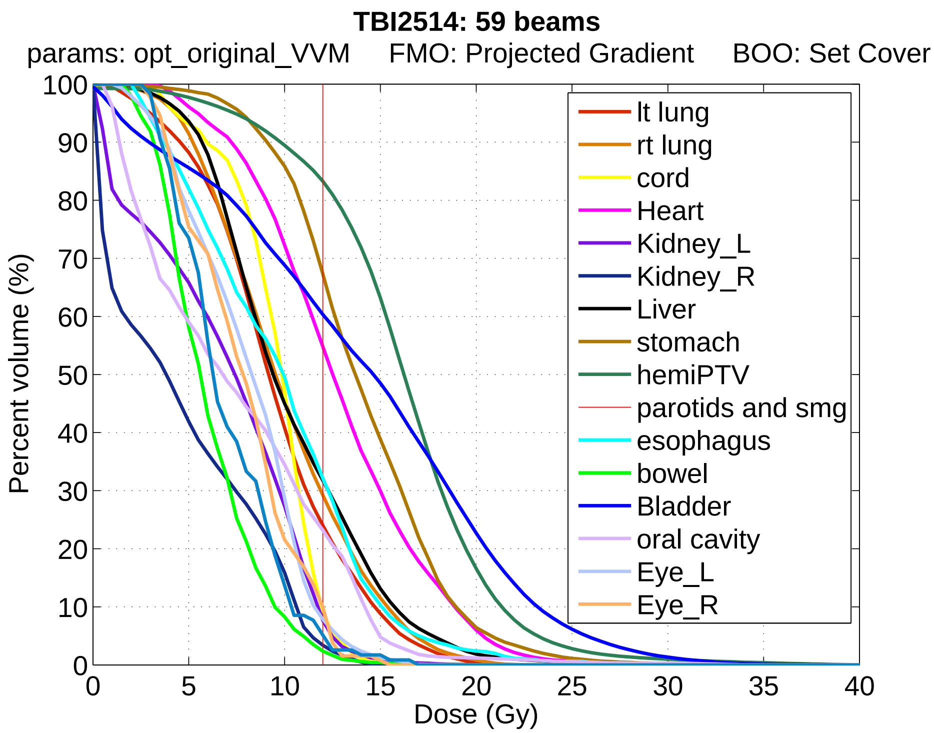

Figure 3: The DVH showing the result of FMO solver, case 1 based on BEV scoring

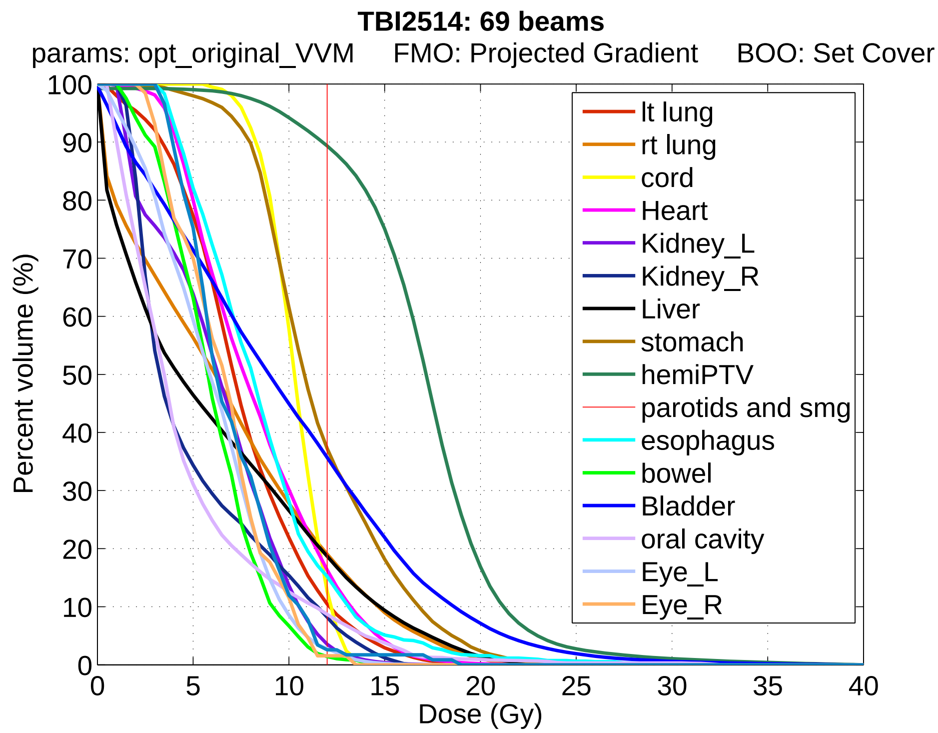

Figure 4: The DVH showing the result of FMO solver, case 2 based on BEV scoring

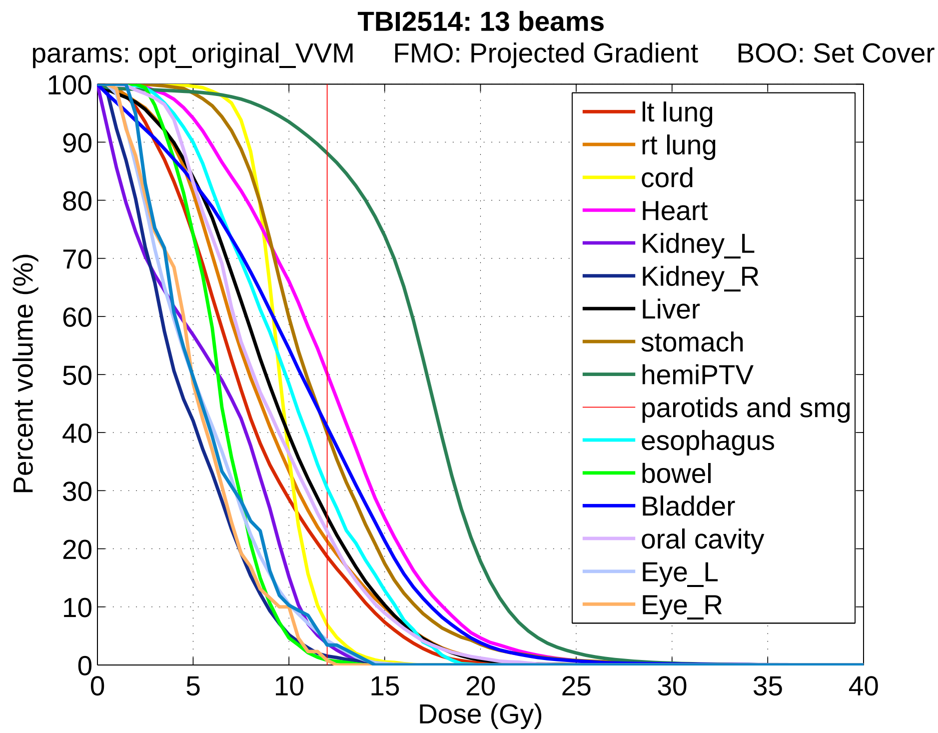

Figure 5: The DVH showing the result of FMO solver, case 1 based on pBEV scoring

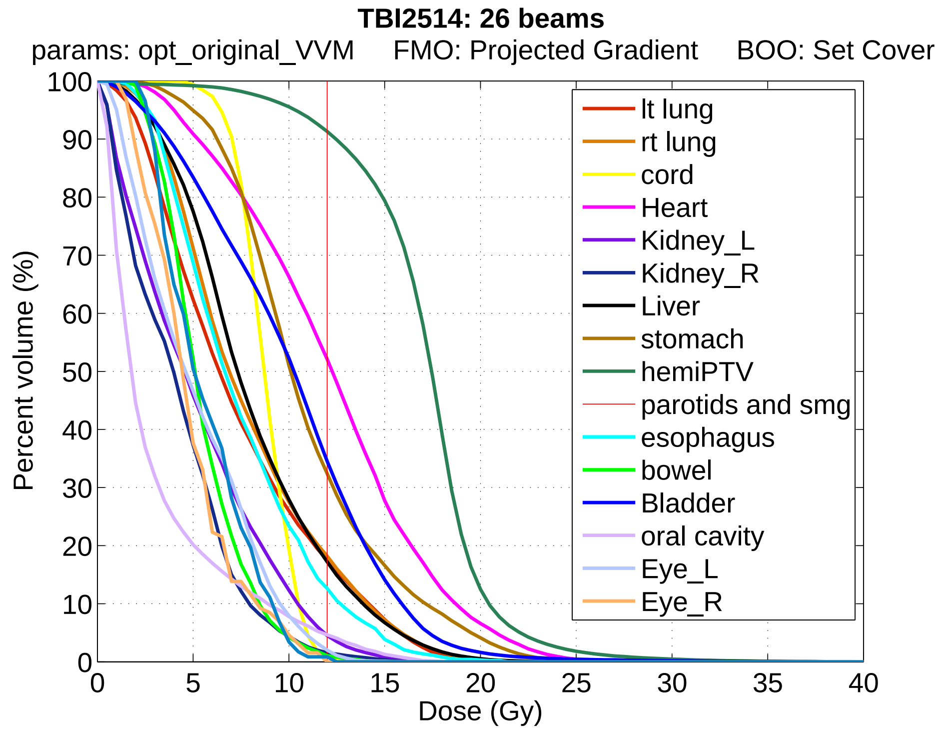

Figure 6: The DVH showing the result of FMO solver, case 2 based on pBEV scoring

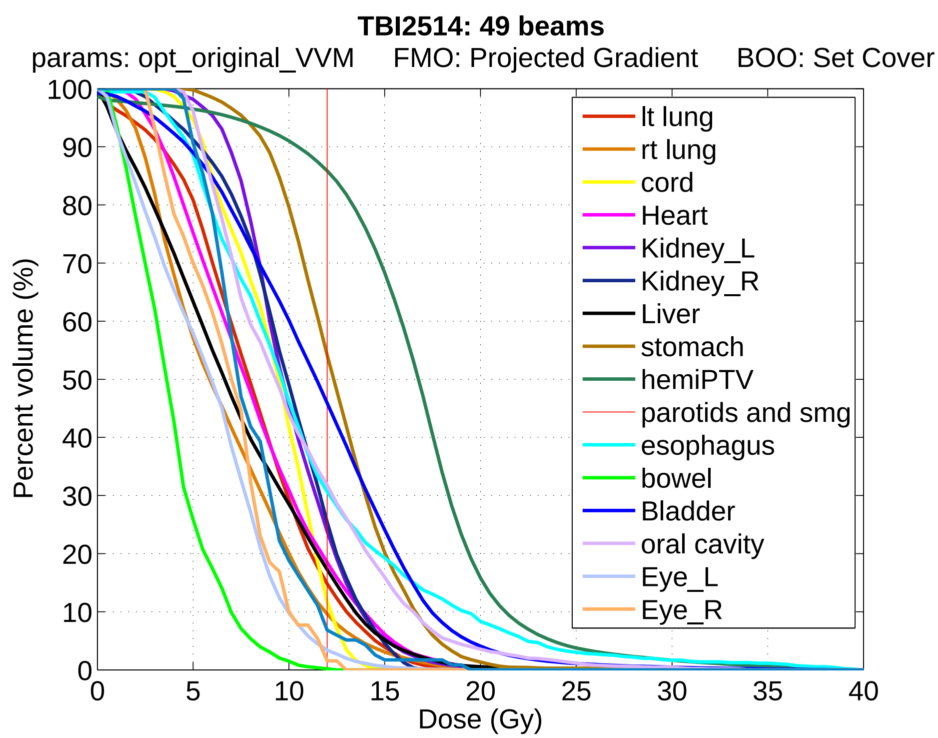

Figure 7: The DVH showing the result of FMO solver, case 1 based on MOD scoring

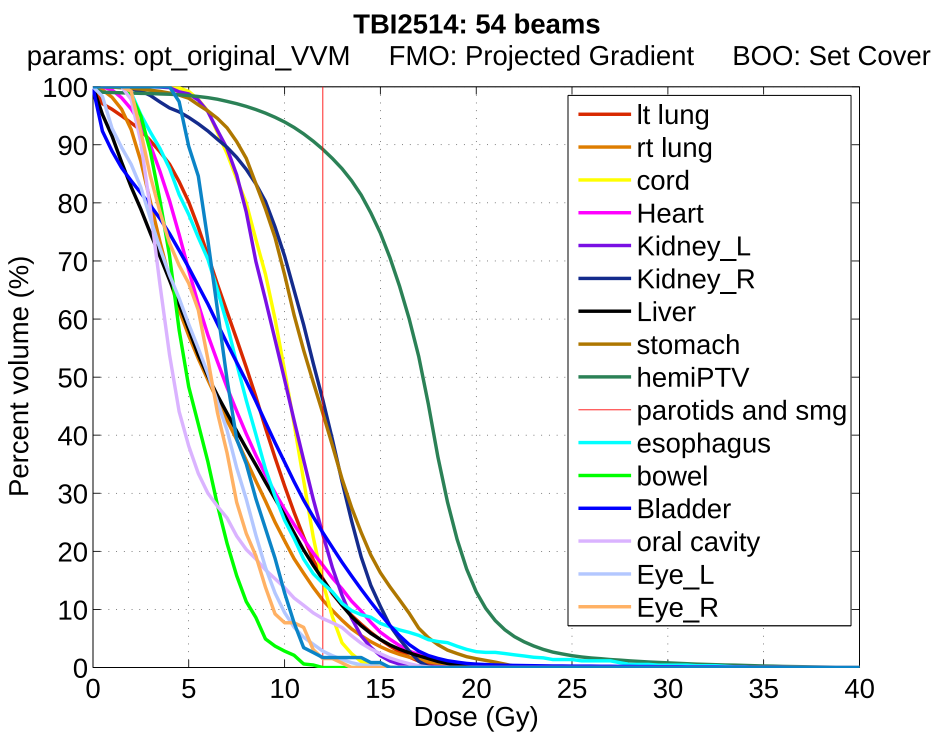

Figure 8: The DVH showing the result of FMO solver, case 2 based on MOD scoring